INFANTS AND CLINICAL RESEARCH: LEGAL AND ETHICAL PERSPECTIVES

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DECLARATION

I declare that the work presented in this thesis is original. No portion of this work has been submitted in support of an application for degree or qualification of this or any other University or Institute of learning. Where the works of others have been used, references have been provided, and in some cases, quotations have been made. It is in this regard that I declare this work as originally mine. It is hereby presented in fulfilment of the requirements for the award of the degree of LLM by Research.

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DEDICATION

This thesis is dedicated to my father Ng Keng Hoong and my mother Teh Ai Lay. You have always taught me that I could achieve anything if I set my mind to it, and all that you have instilled in me has led me to many achievements in this lifetime. For each and every one of those achievements, I owe to both of you.

Thank you for your love, your endless support and encouragement and for always believing I can reach for the stars.

"It is not because things are difficult that we do not dare; it is because we do not dare that they are difficult"

Seneca, Roman Philosopher

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ABSTRACT

This thesis presents an overview of legal and ethical aspects in relation to infants involved in clinical research. The future health of infants and children depend on clinical research which is an important part of medical progress. This thesis will show that there is a need for research involving infants but there are gaps in the current legal and ethical framework which are not readily applicable to research involving infants. There exist a mismatch between what is practised in relation to clinical research involving infants and the current regulatory approach. This has contributed to a lack of understanding and conflicting interpretations as to the way in which research is being conducted in this vulnerable population. There are significant challenges in trying to achieve a balance between what is socially good and the obligation to protect infants who participate in research. The principles of best interests standards and how it is applied in the context of research involving infants is explored. Therefore, the thesis aims at capturing the underlying legal, regulatory and ethical perspectives related to research involving infants and draws together key conclusions on how we might address the identified gaps in the current legal and ethical framework.

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CHAPTER 1: INTRODUCTION

For medicine to continue to save and/or better the lives of individuals, experimentation with human subjects is an absolute must. New drugs, new equipment and new methods that can transform people's lives for the better now and in the future have to be tested on live subjects in the present. That testing has to be conducted within ethical frameworks that ensure the safety of participants. This is nowhere more important than in medical research on children and infants and yet, as this thesis testifies, there remains a paucity of legal and ethical guidance on how research involving infants should be conducted and how parental rights and responsibilities are determined when allowing their infants to participate in research.

As a paediatric clinician and an academic researcher, I have recruited hundreds of infants and preterm neonates into therapeutic and non-therapeutic research studies with the scientific aim of improving our knowledge to benefit future populations of infants. There are large numbers of non-therapeutic research studies currently recruiting infants and preterm infants to study the genetics of disease, pharmacokinetics of drugs or physiological studies of hormonal effects that offer no direct benefit to the individual participants.[1] My personal experience of recruiting infants in therapeutic and non-therapeutic clinical trials, and the processes involved in the ethics and consent procedures as a researcher, have led me to question the application of current research regulatory guidance and the ethical/ legal framework for conducting research involving infants. As a clinician, I have encountered difficulties in the context of research involving infants. If the central aim of global ethical principles should be to ensure that any decision is child-centred and that it should protect the infant's rights to the maximum extent possible, then our current research organisations and application of clinical therapeutic and non-therapeutic trial set-ups using research regulatory guidance raise many questions that appear to conflict with existing ethical and legal principles.

[1] For further information on these areas of study, inter alia, see: (1) www.bapm.org/trials/trial.php; (2) www.ukctg.nihr.ac.uk/trialdetails/NCT01319435; (3) Ng SM, Turner MA, Gamble C, Didi M, Victor S, Manning D, Settle P, Gupta R, Newland P, Weindling AM. (2013) 'An explanatory randomised placebo controlled trial of levothyroxine supplementation for babies born <28 weeks' gestation: results of the TIPIT trial', *Trials*, 14: 211; and (4) The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups (2013) 'Oxygen saturation and outcomes in preterm infants', *N Engl J Med*; 368: 2094.

The Declaration of Helsinki states that "in medical research in human subjects, considerations related to the well-being of human subjects should take precedence over the interest of science and society".[2] The foundation of this approach when applied to research involving infants is to ensure the protection of infants as research subjects within this vulnerable population. However, there exists a mismatch between what we think guidance is and what is practised in relation to research involving infants, raising questions as to the need for current legislation to be more flexible. I will also argue in the next section that research remains an important part of medical progress and infants are a unique population where there is a need for research involving infants to improve their health.

1.1 Why is there a Need for Research Involving Infants?

Alarmingly, there is a lack of medical research involving children and, consequently, over two thirds of children in hospitals are being prescribed unlicensed medications in the absence of such research.[3] The figure rises to over 60% in infant populations.[4] Hawcutt and Smyth (2008) suggest that 50% of medicines used in infants are based on anecdotal data or extrapolated from adult data on medicinal products.[5] This problem is particularly acute because, across the world, up to 80% of drugs that are approved for adults are not approved or labelled for use in children.[6] These statistics raise grave concerns among health professionals involved in the care of children. The extrapolation of data from adults is arguably unsafe and necessitates testing in infants and children, whether it is a novel agent or studying the pharmacokinetics of existing medicines in order to make drugs safer. Children are often prescribed drugs that have only been tested in adults, even though children often respond differently to such medicines. The extensive use of drugs not licensed to treat children has led to the

[2] *World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (2000) (6th version, adopted in South Korea October 2008) Edinburgh WMA [herein after "World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects"].

[3] Hawcutt DB and Smyth RL. (2008) 'Drug development for children: how is pharma tackling an unmet need?' *IDrugs*, 11(7): 502-507.

[4] Ibid.

[5] Ibid.

[6] Hawcutt DB and Smyth RL. (2008) 'The new European regulation on pediatric medicines: regulatory perspective', *Paediatric Drugs*, 10(33): 143-6.

conclusion that children are already being used as research subjects, but without the controlled supervision of a clinical trial or a systematic commitment to learn how to use the drug.[7] There has been widespread criticism that perhaps unethical research is being carried out without any form of legislation. Such "unlicensed drugs" or "off-label use" means that a drug is being used for a purpose within a paediatric population for which it has not been approved by the regulatory agencies.[8]

In the United States, children were not initially included in clinical trials relating to AIDS in the 1990s, with the result that cutting-edge therapies offered to afflicted adults were not made available to younger carriers of the disease.[9] Considering that the choice for these children was either to include them in risky research or to allow them to die from AIDS, it no longer seemed as morally objectionable to include them in clinical trials.[10] This acceptance of children with AIDS as research subjects has given way to a more general acceptance of children as research subjects.

The protection of child health requires that the safety and efficacy of drugs administered to children have been verified by, for example, pharmacokinetic studies. These studies investigate the way in which medicines are absorbed including the route of administration intravenously, orally or topically, the way in which they are excreted and distributed within the body, and the relationship between the dose of medication and the concentration of a medicine in the blood. In pharmacodynamics, developmental changes can also affect the drug receptors that mediate how medicines act in the body. Infants as a group differ physiologically from older children and adults and it is essential that medical research does not exclude this group from the general population.[11] Infants require different medications that are suitable to their needs at the time, and the practice of simply extrapolating treatment regimens and administrations from adults, or simply lowering the dose of the medications administered to the infants merely by estimating

[7] Ibid.
[8] Ibid.
[9] Ibid.
[10] Edwards S and Mc Namee MJ (2005) 'The ethical concerns regarding guidelines for the conduct of clinical research on children', *Journal of Medical Ethics*, 1: 421.
[11] Studies in 2011 show that the use of unlicensed and "off-label" medicines in children is widespread. It was reported that between 50-80% of the medicines currently administered to children have neither been tested nor authorized for their use in the paediatric population which represents approximately 25% of the whole European population. See Knellwolf AL (2011) 'Framework conditions facilitating paediatric clinical research', *Italian Journal of Paediatrics*, 37: 12.

the infants to the proportionate weight and size of the adult, is unacceptable. In the area of pharmacokinetics, research is required to study the formulations of drugs and to determine the pharmacokinetic and pharmacodynamic parameters of drugs in different age groups. These studies are critical and morally obligated in paediatric care because they provide the basis for different formulations of drugs for children that avoid the dangers of either toxicity or under dosing based on extrapolation from studies conducted in adult populations. Determining how children's development affects drugs in the body is both a major rationale and a significant challenge for paediatric research. Such research protocols must be generally conducted in children as data cannot be safely extrapolated from adult studies. Medicinal products that show non-linearity in terms of absorption, distribution and elimination may require a steady state study protocol often involving 24 to 36 hour time intervals of scheduled blood sampling following a dose administration in neonates, infants or children.[12] Children are usually not subjected to dose escalation studies. However, such studies are essential in answering questions of patho-physiological factors that cause dose-concentration changes, to what degree the appropriate dose of medications should be given to provide effectiveness and avoid harm in this population.

Clinical research is also needed in infants because certain medical conditions - such as prematurity and their related complications - only affect infants and neonates.[13] We will never know if adult tested medications or drugs are safe for children and infants unless medical research is undertaken to investigate their effectiveness and safety. The long-term surveillance of drug effect on safety, growth and development are equally important to monitor and such surveillance can only be done in this age cohort. The legality of such non-therapeutic trials remains debatable in view of the ethical problems in repeated blood sampling required with no direct benefit to the infants participating in such non-therapeutic research. However, research is needed to improve the delivery of such medication to infants, for instance either to improve compliance via the route of administration or to identify alternative routes to reduce associated side effects. It can

[12] Ceriotti F, Hinzmann R, and Panteghini M. (2009) Reference intervals: 'the way forward', *Ann Clin Biochem*, 46 (1): 8-17.

[13] Choonara I and Conroy S. (2002) 'Unlicensed and off-label drug use in children: implications for safety', *Drug Safety*, 25: 11. A study of the *Physicians' Desk Reference* showed that there was a 39% decrease in the number of prescription entities licensed for the neonate between 1998 and 2007. See Young L, et al., (2008) 'Access to prescribing information for paediatric medicines in the USA: post modernization', *British Journal of Clinical Pharmacology* 67(3): 341.

also be argued that participation in non-therapeutic drug research may benefit the participant in the foreseeable future should they require the use of the medication that was being studied.

1.2 Aims of the Thesis

This thesis will argue that there is a need for research involving infants but that there are gaps in the basic legal and ethical framework relating to infants in research. The current framework is not sufficiently adapted to infants or flexible enough to respond to the needs of infants, and research and the broad principles such as best interests are themselves subject to a high degree of interpretation. This thesis will concentrate on the population of infants and will critically explore the best interests standard in relation to clinical research. The general statements of research principles that currently exist are generic to research involving children but are not readily applicable to research involving infants. Infants are unique as a research group and they undergo striking maturational changes following birth. Infants are also completely vulnerable and are unable to express their fears, needs or defend their own interests: they are dependent on their parents and guardians to act in their best interests. Potentially any adverse effects they experience from participation in clinical research may substantially impact on their development and education, and certain adverse effects from the research may cause long-term harm such as impairing growth and development.

Since the 1950s, medical research has substantially improved the lives of tens of thousands of infants by the development of vaccines for polio and measles.[14] The successful eradication of smallpox was based on medical research.[15] Treatments that are safe and effective for adults may be dangerous or ineffective for children. For example, radiation therapy can disrupt normal tissue recovery, maturation and development in children if given at inappropriate doses that may be used in adults. This presents a dilemma as to how we make medications and drugs safer for children and infants while not being able to eliminate the potential for harm to children and infants who are

[14] Wehrle PF and Wilkins J. (1981) 'Immunizing agents: potential for controlling or eradicating infectious diseases', *Annu Rev Public Health*, 23: 363-395.
[15] Stuart-Harris C. (1984) 'Prospects for the eradication of infectious diseases', *Review of Infectious* Diseases, 6(3): 405-411.

research participants. Should we stop recruitment that may be of benefit to the individual? Should research involving infants cease if there are no direct or obvious benefits to the individual? How do we quantify risk to the infants who are recruited without knowing the nature of the future risk (especially when the risks or benefits are unknown)? To what extent can absolute permission be given by parental consent or assent for a child to participate in the research which carries a risk of harm and offers no direct medical benefit? Are there potential conflicts between the concept of the infant's welfare and parental authority? It is these questions that are so central to this thesis.

Infants lack capacity to consent and therefore are unable to meet the standards of making any decision for themselves. This means that medical interventions and decisions on whether to embark on them are decided by medical practitioners, researchers and parents. To set the scene for the analysis that follows, Chapter 2 will outline the different contexts within which research involving infants is conducted, drawing a distinction between the types of clinical research and, in particular, between therapeutic and non-therapeutic research. It will also discuss whether participation of infants in non-therapeutic research is ever justified. Chapter 2 then presents a quick historical overview to chart the evolution of laws that govern research involving children. In particular, it covers the unethical experimentations on children during World War II,[16] as well as the Nuremberg Code in 1947,[17] the first major international document to provide guidelines on research ethics. It also discusses how current social, legal and medical influences have given rise to a presumption in favour of children's participation in clinical trials and examines the need for an ethical framework to guide decision-making in this context. Chapter 3 considers the role and principles of the current ethical and regulatory framework in providing the basic standards with which medical research involving infants should comply. It is argued that in the context of research involving infants, the global standards on the rights of the child lack consensus and directionality as there are particular difficulties in the application of these principles and standards within the specific context of medical research involving infants. This will provide the framework for examining the legal and ethical implications of recruiting infants into clinical trials in the present day. It will also show that that there is currently

[16] *Trials of war criminals before the Nuremberg military tribunal: part 3* (1946) London: His Majesty's Stationary Office, 44.
[17] 'The Nuremberg code', *Journal of Law, Medicine and Ethics* (1991) 19(3-4): 266.

an absence of legal and ethical guidance on research involving infants which has contributed to a lack of understanding and conflicting interpretations as to the way in which research should be conducted in this population.

Chapter 4 moves on to explore parental rights and responsibilities in relation to research, and will discuss what is acceptable risk to infants during the conduct and participation in research and how it may contradict the best interests standard which is central to children's rights discourse. Chapter 5 discusses the obligations of informed consent and explores whether infants' rights are truly adhered to in the consenting procedures within the current research regulatory framework. Chapter 6 further explores arguments in support of and against the concept of best interests in the light of more utilitarian arguments when applied to research involving infants. Utilitarianism in this setting explores the logic for the need of participating in research to benefit society and similar populations of infants. While this is not a key focus of the thesis, the discussion on utilitarianism judgements versus best interests of the individual using *Bland and Re A* cases support the broader analyses of current ideologies in clinical research pertaining to infants. Chapter 7 seeks to review and make recommendations as to how some of the identified gaps in the legal and ethical guidance for research involving infants might be addressed. Finally, Chapter 8 draws together the key conclusions of this research.

A central tenet of this thesis is that the core principle of the best interests standard is in conflict with the regulatory research framework that is currently applied to infants particularly within non-therapeutic research. The thesis reveals how a simplistic application of the best interests principle in research involving infants will have a detrimental effect for this vulnerable population. The best interests standard is difficult to apply in its entirety and, arguably, the concept of infants' rights cannot be sensibly applied as they lack capacity. Furthermore, taking an absolute view of the principal standard will ultimately stop research involving infants and deny this population any medical progress in the future. A more wider principle may recognise that infants have rights and these may also be extended to the right to adopt a utilitarian approach by allowing parents the right and responsibility to make informed decisions regarding enrolling their infants into research such that their infants' interests are not undermined but complement the interests of society more generally. Such an approach can be

reconciled with the best interests principle if a ‘global’ perspective of the best interests of all infants is adopted and it can be justifiable within the conduct of the research involving minimally invasive procedures with trivial risk and discomfort that are short-lived. Further, there is a need for more elaboration of current standards and the development of more robust ethical and legal frameworks surrounding the decision-making processes and conduct of research involving infants.

CHAPTER 2: THERAPEUTIC AND NON-THERAPEUTIC RESEARCH AND A HISTORY OF CLINICAL RESEARCH ON CHILDREN

2.1 Types of Clinical Research

There are two types of clinical research - therapeutic and non-therapeutic research - yet there are no authoritative definitions for either of these terms. Generally speaking, *therapeutic research* consists of studies that have a therapeutic intention and are trials which recruit patient subjects and provide a specific form of treatment to the patients to study its impact on a particular disease. *Non-therapeutic research* does not provide a treatment for the participants but instead focuses on aspects of the particular disease and how it progresses.

Within clinical trials, evaluation of new treatments is defined by three different phases. *Phase I* studies are the most basic of clinical trials where the drugs are tested to evaluate the dosages and effect of the treatment, and whether the treatment can be administered and what the maximum tolerated dosages are. Drugs are often given at gradually increasing dosages until there are unacceptable side effects.[18] As it remains unknown whether the treatment will be effective against a particular disease, people with a variety of diseases are often enrolled so Phase I trials are often classed as non-therapeutic research as the participants are, as Foster (2009) notes, true 'guinea pigs' as the research has no therapeutic benefit and the 'researcher' does not intend to treat the research subjects.[19] In *Phase II* studies, the results from Phase I studies are implemented to patient subjects and the treatment is targeted towards patients who have responded most favourably in Phase I trials. *Phase III* studies are those trials that will progress to further test the standard treatment (or current best) against the conventional treatment or alternatives of the intended drug.[20] Phase III trials are those that most children will participate in. The most commonly performed research are therapeutic clinical trials which evaluate medical therapies on patients in a strictly controlled manner and the

[18] UK Medicines for Human Use (Clinical Trials) Regulations /SI 2004/1031
[19] Foster C (2009) *The Ethics of Medical Research in Humans*, Cambridge University Press: Cambridge, 89.
[20] Ibid.

purpose of such trials is to determine whether or not the treatment options are safer, better or more effective than the current standard care. Ethically, therapeutic controlled trials are more justifiable to conduct as it is required to clarify the efficacy or safety over the standard care, and as such, the subjects stand to benefit from being a participant in the research.

In these therapeutic clinical research trials, the treatment that is the subject of the clinical research is compared with conventional available treatment. In other randomised controlled trials, for conditions having no effective treatment available, the control regimen to which the new treatment is compared is usually either an observation or administration of a placebo which is a substance or medication that has no therapeutic effect, used purely as a control. It has been argued that placebo-controlled trials may be ethically conducted as long as there is no known effective therapy that exists for the condition and as long as omission of such treatments would not increase risk of death or irreversible morbidity, and patients are fully informed about their alternatives.[21] For example, in TIPIT - a randomised controlled trial of thyroxine supplementation in extreme preterm infants[22] - there was clinical uncertainty about whether apparently low plasma FT4 concentrations which are commonly found in these preterm infants should be treated or not with thyroxine supplementation to improve neurodevelopment. The current practice for these infants was to offer no treatment or supplementation with thyroxine, because it remains unknown whether the infants may or may not benefit from thyroxine. Therefore it was justifiable to conduct this trial with infants recruited to either the treatment arm or the placebo arm.

2.2 Judicial Interpretation of Therapeutic Research: Simms v Simms

The judicial view of therapeutic research can perhaps be best illustrated from the case of *Simms v Simms and An NHS Trust*.[23] Jonathan Simms, an 18 year old male patient from Belfast, was diagnosed with a new variant of Creutzfeldt–Jakob Disease (CJD), a degenerative neurological disorder of the brain that is invariably fatal. There

[21] Reynolds T. (2000) 'The ethics of placebo-controlled trials', *Ann Intern Med*. 133:491-2.
[22] It should be noted I was the primary grant holder and researcher on this project. See, for further information, Ng SM, et al., (2008) 'Tipit: A randomised controlled trial of thyroxine in preterm infants under 28 weeks' gestation', *Trials*, 9(17): 137.
[23] *Simms v Simms* [2003] 1 All ER 669

was no recognised treatment or cure available, but overseas medical research had identified a novel treatment which inhibited the formation of abnormal protein prion in animal studies. His parents wanted him to receive that experimental treatment which, at the time, had not been previously tested on humans. Expert committees of the Department of Health (DoH) and of the local NHS Hospital Trust refused to approve the therapy sought. Both the DoH's CJD Therapy Advisory Group and the Committee on the Safety of Medicine's views were that given the lack of data on safety and effectiveness, there was no logical basis for prescribing experimental protein prions in cases of CJD and it was further recommended by the expert committees that animal trials were necessary before the advice could be changed. Jonathan's parents sought declarations that their son lacked capacity to consent to treatment and that it was lawful as being in their best interests for them to receive the proposed treatment. The Courts held that the parents could consent to a novel treatment that has been used in experimental research given that there was no alternative treatment available. The decision in this case was significant for three key reasons: first, it recognised that doctors have a certain leeway to use therapies that have not yet been fully tested as to safety or efficacy; second, it specifically permitted such innovative and unproven therapies or treatment even where the patient is incompetent; and, third, it confirmed the tendency of the Courts to evaluate and in certain cases reject the views of medical experts on the appropriate use of health care resources.[24] The Courts therefore formed a relational view of the best possible interests for the patient who lacked capacity, taking into account the practical attitude and wishes of the patient's relatives which then set the parameters of decision-making concerning using experimental and unproven therapies in a clinical situation that was proven to be incurable and eventually fatal.

Although the *Simms* case does not provide any authority in relation to justification of randomised controlled trials or experimental research, can the reasoning behind the *Simms* case be transposed to any research so that if there is a possibility of benefit to the subject it is lawful to proceed with the trial? Some may argue that the *Simms* case cannot be applied analogously to any other situations as it was a desperate situation with little to lose and the judgment only provided guidance on what may be

[24] Harrington JA. (2003) Deciding best interests: medical progress, clinical judgement and the good family, *Web Journal of Current Legal Issues*, http://webjcli.ncl.ac.uk/2003/issue3/harrington3.html

lawful, not what may be ethical.[25] As stated in the introduction, there is a paucity of legal and regulatory guidance relating to infants who are incompetent and incapable of giving assent for research and, at present, infants are being recruited to both therapeutic and non-therapeutic research because it is recognised that there is a need for research in this population. Conversely, it may not be ethically justifiable that therapeutic research participation may significantly harm or cause significant distress to the infant as a research subject. The British Medical Association (BMA) in 2004 stated that where a child is deemed as incompetent by age or illness, the parent(s) or legal guardian(s) will be able to consent to therapeutic research.[26] The decision of the Court in *Simms vs Simms* to allow this experimental novel treatment was not reached from any reasonable logic because such an experimental treatment had never been tested full for safety nor efficacy. The case illustrates that a kind of common sense judgment was undertaken in an unusual case which was dependent to a significant extent on the reasoning of the deciding judge. It is argued here that the judge provided a lawful reasoning to achieve the desired result from a difficult situation.

2.3 Is Non-Therapeutic Research Justified?

Non-therapeutic research trials are trials that do not provide any treatment benefits to the subjects, but instead seek to study important factors which may help advance the understanding of a disease, its impact or its progression.[27] For example, non-therapeutic studies may look at collection of tissue specimens to examine the cell structure of a form of cancer, or may collect blood samples to understand the effects of pharmaco-dynamics of certain drugs. Other studies may track epidemiological information such as the long-term health effects of chemotherapy or collect DNA to better understand the genetics of the disease. Non-therapeutic trials offer no personal benefit to the individuals who participate compared to therapeutic trials. The principle therefore that clinical research involving children should confer a direct personal benefit

[25] Kennedy I and Grub A, eds., *Medical Law (*Butterworths, London, 2000), 213.
[26] British Medical Association, *Medical Ethics Today: The BMA Handbook of Ethics and Law* (BMA, London, 2004), 132.
[27] Yeung, V. (2007) 'Clinical trials in children', in I. Wong, C. Tuleu, I. Castelllo, V. Yeung, & P. Long (eds.),*Pediatric Drug Handling* (Pharmaceutical Press, London), 85-115.

to the child and that the interests of the child must prevail over the interests of science or society cannot apply to non-therapeutic research.[28]

In the Declaration of Helsinki,[29] first issued by the World Medical Association's Committee on Medical Ethics in 1964, a need was recognised for professional guidelines designed by physicians for physicians to define diagnostic and therapeutic methods of experimentation. Medical research was classified into two groups: 'experiments in new diagnostic and therapeutic methods' and 'experiments undertaken to serve other purposes than simply to cure an individual'. The Declaration was an authoritative and influential source of guidance for researchers involved in scientific research with human subjects and attempts were made to distinguish between therapeutic research and non-therapeutic research, in various terms of the Declaration and guidance. However, the most recent version of the Declaration (2008) removed that explicit distinction between therapeutic and non-therapeutic research.[30]

There were arguments against the revisions of the Declaration such as it should remain 'a shield protecting the vulnerable, children, the senile and the mentally handicapped', and that despite the difficulties in defining therapeutic and non-therapeutic research, in practice it was very useful to distinguish if research was intended to benefit an individual research subject or not, and therefore making it useful for research ethics committees in assessing research protocols.[31] The editor of the British Bulletin of Medical Ethics, Richard Nicholson, stated that "in what seems sadly to be American bioethical imperialism, the World Medical Association's Committee on Medical Ethics wants to make life easier for American researchers, and such a proposal was born of the self-interests of American researchers, and not the interests of medical research worldwide".[32] Nicholson further argued that "to satisfy the perceived needs of the American researcher and to change the document completely, was for the sake of a

[28] UK Medicines for Human Use (Clinical Trials) Regulations /SI 2004/1031
[29] The evolution of the Declaration of Helsinki is covered later in this chapter, however, it is introduced here for the purposes of the current discussion on whether non-therapeutic research is justifiable.
[30] World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. See Article 27, (6th version, adopted in South Korea October 2008) and Article 17 of the Council of Europe, Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Oviedo, 4.IV.1997).
[31] Nicholson RH. (2000) 'Editorial', *Bull Med Ethics*, 1: 160.
[32] Ibid.

small bunch of American researchers, who want greater freedom to behave unethically".[33]

On the contrary, the main arguments for the revision of the Declaration that ultimately constructed the 2000 version was that the previous edition did not keep abreast with changing research activities and the distinction between therapeutic and non-therapeutic research was an impracticable and unfeasible one that could lead to undesirable consequences. Levine[34] argued that the Declaration of Helsinki was a flawed document in that it relied on the illogical distinction between therapeutic and non-therapeutic research. For Levine, research cannot be meaningfully divided into a therapeutic or a non-therapeutic category because it is unclear whether such labels refer to the project as whole or to the individual participants. Some research projects benefit certain individuals but not others as in randomised controlled trials where the control participants have no benefit. It may be wrongly presumed by others that therapeutic research confers a benefit and that non-therapeutic research confers none, yet the risk of harm in therapeutic research may be considerable, and the risks involved in non-therapeutic research is negligible.[35] It remains difficult to define regulatory parameters of research because of such vague definitions.

In October 2000 the VI-version of the Declaration of Helsinki was adopted unanimously following a prolonged and protracted consultation, and the document was finalised without the explicit distinction between therapeutic and non-therapeutic research. The removal of the non-therapeutic category in the final 2000 version was replaced with a new category related to 'additional principles for medical research combined with medical care' to highlight the fact that where research was combined with medical care, additional measures should be undertaken to ensure the safety of human participants in research. It was argued that although the language had been removed, the concept stayed the same.[36]

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[33] Ibid.
[34] Levine RJ. (2000) 'Some recent developments in the international guidelines on the ethics of research involving human subjects', *Ann N Y Acad Sci*, 2: 918.
[35] Ibid.
[36] Mason S and Megone C. *European Neonatal Research: Consent, Ethics Committees and Law* (Aldershot: Ashgate, 2001), 4.

It can be argued that the construction of the 2000 Declaration in relation to the boundary between therapeutic and non-therapeutic research means that such vagueness and difference in interpretation and demarcation of what constitutes therapeutic or non-therapeutic research allows for negotiations to occur from organisations carrying out medical research and grants them a varied degree of interpretative license. Ratification of the first version of the Declaration of Helsinki and the subsequent amendments in 2008 that followed resulted in a poorer demarcation of therapeutic research and non-therapeutic research. This had an impact on research practices and the context on the efforts to obtain and maintain credibility and legitimacy to perform research with human subjects, particularly in the case of the boundary between therapeutic and non-therapeutic research. Different sectors such as the scientific human research practices, regulatory bodies and research ethics committees will face greater debate on defining the boundaries between therapeutic and non-therapeutic whilst other groups may make the document workable in a strategic manner.

2.4 A History of Clinical Research Involving Children

2.4.1 Lessons from Nuremberg

The previous section notes the lack of a clear distinction between therapeutic and non-therapeutic research, and that both forms of research continue to be conducted in infants who lack capacity. This section explores the history of how clinical research evolved to include children. The 1947 Nuremberg Code[37] stated that voluntary consent is a requirement in clinical research studies, emphasising that consent can be voluntary only if research participants are able to consent, they are free from any coercion and that they comprehend the risks and benefits of research participation. The Code also states that "researchers should minimise risk and harm, and to ensure that such risks do not significantly outweigh potential benefits, use appropriate study designs, and guarantee participants' freedom to withdraw at any time".[38] Prior to the Nuremberg Code, there was no universally accepted code of conduct governing the conduct and ethical aspects of human research. The code was a result of unethical clinical experimentation on war-

[37] 'The Nuremberg code', *Journal of Law, Medicine and Ethics* (1991) 19(3-4): 266.
[38] Ibid.

time prisoners during World War II.[39] In World War II in Germany, human hypothermia experiments were conducted with unwilling civilians, many whom were children. Scientific data was carefully recorded and noted and such experiments occurred with the support of the German government at the time.[40] The ethical dilemma arises of whether such data should be used and the implications of using such data became a discussion point. Should the data be referenced as they were in the past or should they be destroyed forever? For scientists, some would argue that the questions are irrelevant as the data was gathered from the culmination of a scientific inquiry by a government at the time. Researchers from all over the world have used and referenced the Dachau hypothermia experimentation data since its discovery in 1946.[41] Regardless of the motivation, the data remained valid in its scientific inquiry and was not found to be erroneous. To use such data in today's scientific domain would reinforce the Nazi philosophy that there is a differential value amongst human beings. The argument is that the data in any form should not be used in any sort of scientific benchmarking as this would imply that the human subjects who died from these experiments were merely physiological entities in a research study. The appropriateness of using such unethical data continues to be debated and to this day, some of the data from Dachau had been extrapolated for use in hypothermia cooling for the treatment of infants and neonates with hypoxic-ischemic encephalopathy to reduce neurodisability.[42] The controversy on whether one should even use data in any form based on the ethical arguments would suggest that a scientist is only influenced by his or her own personal ethical viewpoint. If scientists pursue the kinds of research conducted based on personal philosophies without ethical considerations, then how do we stop them from exploiting human subjects to advance their scientific understanding or knowledge? Ethics and the law will remain the only guidepost for scientists and researchers to conduct appropriate research.

2.4.2 Declaration of Helsinki

As noted earlier in this chapter, in 1964 the Declaration of Helsinki established a statement of ethical principles to provide guidance to physicians and other participants

[39] Ibid.
[40] Ibid.
[41] *Trials of war criminals before the Nuremberg military tribunal. Part 3.* (His Majesty's Stationary Office, London, 1946).
[42] Pfister RH and Soll RF. (2010) 'Hypothermia for the treatment of infants with hypoxic-ischemic encephalopathy', *Journal of Perinatology*, 30: suppl 4.

in biomedical research involving human subjects.[43] The Declaration serves to bind researchers and physicians with the statement "the health of my patient will be my first consideration" and declares that "a physician shall act only in the patient's interests when providing medical care which may have the effect of weakening the physical and mental condition of the patient". It was established to supplement and correct the perceived deficiencies within the Nuremberg Code with particular reference to physician-led research and patients. The Declaration of Helsinki was adopted[44] and went further than the Nuremberg principles in the respect owed to each individual in medical research, and that the well-being of the human subject must take precedence over the interests of society and science. Further revisions of the Declaration of Helsinki in 1975, 1983, 1989, 1996, 2000 and 2008 were published and permit the participation of children in research with parents making the decision to consent on behalf of the child. The Declaration also governs international research ethics and defines rules related to research in human subjects. The purpose of any biomedical research involving human participants must be to improve diagnostic, therapeutic and interventional procedures understanding the aetiology and pathogenesis of the disease. The Declaration, however, remains silent on how its principles relate to research involving infants, the growing recognition of infants' rights and that their best interests and perspectives should also be taken into account.

2.4.3 Research Changes towards Involving Children in Recent Years

In 1963 the British Medical Association (BMA)[45] in the UK stated that all children can participate in therapeutic research, but children younger than 12 years were not permitted to participate in non-therapeutic research. In the 1990s, there were advocates for children's voices to be heard and for children's opinions to be sought in any matter that involves them.[46] The focus was then on research in older children who had the capacity and understanding to articulate their views. In 1991, revised guidelines were issued by the BMA and British Paediatric Association (BPA) stating that research participation by children that does not directly benefit the child was not necessarily

[43] World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.
[44] Ibid. Ethical research on human subjects must be conducted under the provisions of this declaration.
[45] British Medical Association, *Medical Ethics Today: The BMA Handbook of Ethics and Law*, 138.
[46] Rainer M. (1992) 'Children's voices, adults' choices: children's rights to legal representation', *Family Matter*, 33: 4-10.

unethical or illegal.[47] In the USA during the 1980s, the AIDS drug trials involved participation of children and the debate for access to child subjects and equity to potentially lifesaving medication evolved to permit greater access to using children as research subjects.[48] The last two decades represented a considerable shift in favour of including children as research subjects for drug trials, potentially exposing children to risks without providing direct benefits.[49] Until two decades ago, children were not allowed to be participants of drug research trials simply because they were perceived to be incapable of consent and were therefore vulnerable to abuse from drug trials.[50] The current international, European and domestic legal framework permits and provides guidance for research in children but, as explored in the next chapter, there remains a gap in the current ethical and legal regulatory framework on its application of infants in research.

[47] Royal College of Paediatrics and Child Health, (2000) 'Guidelines for the ethical conduct of medical research involving children', *Archives of Disease in Childhood*, 82(1): 178-182.
[48] Doyal L and Tobias J. (2000) 'Informed consent in medical research', *BMJ Books* 1: 286-292.
[49] British Medical Association. *Medical Ethics Today: The BMA Handbook of Ethics and Law*, 138.
[50] Ibid.

CHAPTER 3: AN OVERVIEW OF THE REGULATORY FRAMEWORK

A range of instruments enacted across an array of regulatory levels provide the framework for research involving children. These include international treaties such as the United Nations Convention on the Rights of the Child (CRC), European Union (EU) legislation that is automatically applicable and therefore binding at domestic level, and the common law of tort.

The medical societies and research ethics committees have produced research and ethical guidance on infants and children which is non-binding, and critical care decision making in fetal and neonatal medicine have also been established by the Nuffield Council on Bioethics Working Party to provide advice on the ethical, social and legal issues that arise in critical care of fetuses and infants.[51]

This chapter addresses each theme of the regulatory framework which makes up our current research and ethical framework. The chapter will show that although the current framework discusses aspects of research in children and how decisions are made on behalf of a fetus or a baby, none of the current guidance or framework is specific to research involving infants, exposing a significant regulatory gap for this vulnerable group of research subjects.

3.1 United Nations Convention on the Rights of the Child (CRC)

3.1.1 Overview of the CRC

The CRC was devised to set out a comprehensive legal and ethical framework related to the rights of the child. It is the most widely ratified international convention in existence and it remains a significant document in placing obligations on States signatories to comply with, and to ensure that the domestic or common law reflects its position. It contains an extensive reference of rights, which includes civil and political, social, economic, cultural, recreational and humanitarian rights.[52] The CRC assumes that children's rights are universal regardless of age and it applies to all people under the

[51] Nuffield Council on Bioethics (2006) 'Nuffield Council Critical Care Decisions in Fetal and Neonatal Medicine', *http://nuffieldbioethics.org/wp-content/uploads/2014/07/CCD-web-version-22-June-07-updated.pdf*

[52] McGoldrick D. (1991) 'The United Nations Convention on the Rights of the Child', *International Journal of Law and the Family*, 132: 133.

age of 18 and the UK qualified this to include all children from birth to 18 years old.[53] The CRC is accompanied by a series of 'General Comments' (GCs) relating to specific provisions which offer detailed guidance on how they should be interpreted and applied. While the Comments are not legally binding, they are widely regarded as authoritative.[54] This chapter will focus on the GCs relating to Articles 3, 5, 6, 7 and 24 as a source of how these principles may be used to underpin the issues related to research involving infants.

3.1.2 Best Interests of the Child

Article 3, paragraph 1, of the CRC contains a core principle which states that:

> In all actions concerning children, whether undertaken by the public or private social welfare institutions, courts of law, administrative authorities or legislative bodies, the best interests of the child shall be a primary consideration.

The term "best interests" remains a key principle on which decisions relating to medical research involving infants are often based. It is important therefore, to consider the origins of this concept in legal terms by using the "best interests" test and applying it to research involving infants.[55] It is argued that research cannot be taken as solely based on the best interests of the individual alone, but rather a more relational approach towards public health is required.[56] It imposes a duty on states to ensure that children receive protection and care as is necessary for his or her well-being and, to this end, shall take all appropriate legislative and administrative measures. Article 3 of the CRC gives the child the right to have his or her best interests assessed and taken into account as a primary consideration in all actions or decisions that concern him or her, both in the public and private sphere.[57] It is recognised that children have interests that require protection while they are incapable of taking care of themselves and that others should have that responsibility to do so. The best interests principle is not a right in itself: it is

[53] Committee on the Rights of the Child, General Comment No.7 (2005) *Implementing Child Rights in Early Childhood* CRC/GC/2005/7 and see also UK Reservation and Declarations CRC/C/2/Rev 4 at 32 December 1991.
[54] Payne L. (2009) 'Twenty years on: The implementations of the UN Convention on the rights of the child', *Children and Society*, 23: 149-155.
[55] Elliston SD. The best interest of the child in healthcare (Routledge, London, 2007), 38.
[56] Fox M and Mchale J. (1997) 'In whose best interests?' *Modern law Review*, 60: 700-709.
[57] Ibid.

used in order to implement rights in relation to a particular child and it informs the interpretation of other rights and constitutes one of the four general principles of the Convention.[58] Rights are therefore interpreted and given effect in accordance with the infant's best interests.[59] It is also a guiding principle for those involved in developing law and policy which affect children. This provision is particularly relevant in the context of decision-making for infants involving research because there is no specific or explicit guidance within the CRC on infants and research. The problems with applying the best interests test to research involving infants cannot always be an individual assessment and there are circumstances where a more utilitarian approach has to be adopted. This will be discussed in more detail in Chapter 6.

3.1.3 Children as Right Holders

The human rights approach operates indiscriminately, thereby rejecting the idea that a person must have certain characteristics to have rights.[60] Donnelly states that human rights are the rights one has simply by virtue of being human.[61] The source of human rights is man's moral nature as opposed to man's capabilities.[62] Freeman also states that being a rights-holder "is not dependent on actual autonomy, rather on the capacity for it".[63] Therefore, if this theory holds, both neonates and infants should also have individual human rights, even though they do not have any autonomy and by themselves are unable to exercise or claim their rights. Others would debate whether children should have the same kind of rights as adults or whether their rights should be qualified or enlarged to take into account the specific aspects of childhood such as the need for support and care while they are developing physically, emotionally and intellectually.[64] These issues are of relevance because research is being carried out on infants who cannot assent and yet there is so little concentration on any guidance to

[58] Van Beuren G. *Child Rights in Europe* (Strasbourg, Council of Europe Publishing, 2007), 34.
[59] MacDonald A. *The Right of the Child: Law and Practice* (Bristol, Jordan Publishing, 2011), 24.
[60] Article 2 of the CRC states "Parties shall respect and ensure the rights set forth in the present Convention to each child within their jurisdiction without discrimination of any kind, irrespective of the child's or his or her parent's or legal guardian's race, colour, sex, language, religion, political or other opinion, national, ethnic or social origin, property, disability, birth or other status".
[61] Donnelly J. *The Concepts of Human Rights* (New York, St. Martin's Press, 1985), 1. See also J. Donnelly, *Universal Human Rights: In Theory & Practice* (2nd ed.) (Ithaca, Cornell University Press 2003), 13-16.
[62] Ibid.
[63] Freeman M, *The Rights and The Wrongs of Children* (London, Frances Pinter, 1983), 57.
[64] Eekelaar J. (1994) 'The interests of the child and the child's wishes: the role of dynamic self-determinism', *International Journal of Law and the Family*, 42: 170.

enable infants to participate in research. Article 6 of the CRC states that "every child has the right to life and that States Parties shall ensure to the maximum extent possible the survival and development of the child".[65] The CRC also highlights the importance of thinking of young children as rights holders and independent persons worthy of respect. In General Comment no.7 - *Implementing Child Rights in Early Childhood* - it states:

> The Convention requires that children, including the very youngest children, be respected as persons in their own right. Young children should be recognised as active members of families, communities and societies, with their own concerns, interests and points of view. [66]

3.1.4 Right to the Highest Attainable Standard of Health

Article 24 of the Convention recognises the right of the child to enjoy the highest attainable standard of health, as well as the right to facilities for the treatment and rehabilitation of health. Participation in clinical research involving infants is an important means of promoting the health, progress and well-being of the infant. Infants born at prematurity have different physiology from older children and preterm delivery leads to some unique complications. Non-therapeutic research projects such as those that include systematic investigations of disease processes, research into childhood development, aetiology of diseases in infancy, and careful scrutiny of diagnosing, assessing and treating disease in infants are just as important to validate with research. Research that is therapeutic becomes worthwhile in infants if there are identifiable prospects of benefit to the child and if the research is well designed and well conducted according to ethical and legal guidelines. The Convention makes it clear that in all actions affecting children, a child-centred approach must be taken and the child must be recognised as an independent rights-holder. Infants therefore clearly benefit from CRC rights to protection from abuse, neglect, harm and discrimination.

3.1.5 Parents as Decision Makers

As infants cannot participate in decisions, it is important that those who make decisions for them have the best interests standard as their guiding framework. Article 5

[65] Fortin J. *Children's Rights and The Developing Law* (Cambridge, Cambridge University Press, 2009).
[66] Lyon C. (2007) 'Interrogating the concentration on the UNCRC instead of the ECHR in the development of children's rights', *Children and Society*, 21: 147-153.

of the CRC requires States to respect the responsibilities, rights and duties of parents and other family members as provided for by local custom to present appropriate direction and guidance to children in their best interests. Thus, the role of the principle is to aid those who make decisions for children, such as parents. Parents therefore are entrusted with the primary responsibility to ensure a child's best interests and should a conflict arise between a child's rights to protectionism and parental interests, then in some cases outside intervention will be required that is upheld by the courts. It may be argued that a conflict of interest may arise between what is truly a child's best interests and what is the best interests of the parent or family unit and Family courts have made decisions based on a balancing of probabilities of what they think is the best interests of the child.[67] For example, if parents choose to relocate to a different place or city due to better job prospect offered, at the time it may not be in the best interests of the child who would be uprooted from an environment in which he/she has been thriving, to disconnect with friends and other relatives as a result of the relocation. Yet, the counter-argument would be that it would be for the best interests of the family unit including the child if the better job prospects will lead to an improved standard of living and better future prospects in education for the child. Such interpretations of best interests are often taken in a relational view as in many contexts, in acknowledgement of the interdependency of members of the family, but also to allow parents to make more speculative decisions, based on what they feel will benefit their children in the longer term.

A human rights approach is particularly relevant in the context of medical research. We are compelled to recognise all infants as a rights-holder and, as such, be able to protect them from approaches which could result in the sacrifice of their best interests for the sake of good scientific progress. Their rights have an instrumental role in shaping the means and processes by which policies are developed to uphold human rights.[68] Interestingly, Tobin argues that the aim of the human rights approach is to "insulate rights-holder from claims based on principles of utility, which otherwise would not only be appropriate, but decisive, reasons for public or private action". He discusses a broader issue of adapting a rights-based approach. Tobin also states that:

[67] King M. (2005) 'The right decision for the child', *Modern Law Review*, 70: 857-871.
[68] J. Tobin. 'Understanding a human rights based approach to matters involving children: conceptual foundations and strategic considerations', in A. Invernizzi and J. Williams (eds.) *The Human Rights of Children: From Visions to Implementation* (Surrey, Ashgate, 2011), 89.

> This broader role and value of human rights is a critical feature of a rights based approach. It required a vision of human rights that extends beyond recognition of their legal status to an understanding that such standards embody a particular system of ethical demands that are designed to inform, assist constrain and direct the actions of those actors which have the capacity to impact on the rights of other actors.[69]

This principle is further re-iterated again in Article 18, which sets it out in stronger terms, and states that "parents or legal guardians have the primary responsibility for the upbringing and development of the child. The best interests of the child will be their basic concern". The CRC therefore allows for parents to act as proxy to safeguard the welfare of infants in the decisions that they make, which is not antipathetic to the children's rights. The important role for parental responsibilities and parental decision making in the context of infants' participation in research will be discussed further in Chapter 4.

3.1.6 CRC Principles in Relation to Infants and Research

The CRC, in its vast catalogue of children's rights, does not make it clear where the boundaries lie with the rights of infants in the decision making process for medical research participation.[70] The concept of the child's best interests is aimed at ensuring both the full and effective enjoyment of all the rights recognized in the Convention and the holistic development of the child, and the Committee has already pointed out that "an adult's judgment of a child's best interests cannot override the obligation to respect all the child's rights under the Convention".[71] In Article 3, it is clear that there is no hierarchy of rights in the Convention: all the rights provided for therein are in the "child's best interests" and no right could be compromised by a negative interpretation

[69] Ibid., 101.
[70] MacDonald A, *The Right of the Child: Law and Practice* (Bristol, Jordan Publishing, 2011), 24.
[71] Committee on the Rights of the Child, General Comment No.14 (2013) *On the right of the child to have his or her best interests taken as primary consideration* (Article 3 , para 1) pages 15-17, note. The UNCRC gives children and young people (under the age of 18) specific rights, through 54 articles. These include the right to: a family life; be protected from violence; have a say and be respected; be healthy; and have an education. It also gives extra rights to children and young people living in difficult circumstances such as young people in trouble with the law, young refugees and asylum seekers.

of the child's best interests. Infants have as much rights as older children in their role towards medical research and towards attaining the highest standard of health. Article 6 of the CRC states that "every child has the right to life and that States Parties shall ensure to the maximum extent possible the survival and development of the child".[72] This can be interpreted as being pro-research towards infants' participation in ensuring health, development and medicines for infants continues to improve and progress. Articles 3 CRC, however, appears to go against the practice of involving infants in research where it cannot be proven to be in their individual best interests, nor can the infant express any view in the matters of the research that involves them. How can we reconcile these dilemmas towards infants' participation in research?

Clinical trials in infants are continuing today and consent is being given solely by the mother or legal guardian. Researchers have argued that recent legislation has made it impossible to carry out appropriate research in children and infants even when there is a direct benefit for this group of patients.[73] It is interesting to note that with the advancement of children's rights there has been a change in terminology within the entire discourse of children's rights more generally. The CRC, for instance, refers to rights, responsibilities and duties of states, parents and families. In the past - and to some extent today - the term 'parental power' was commonly used in Welsh and English case law that dealt with parents, their children and the law. Parental power was defined as the "complex of rights, powers, duties and responsibilities vested in or imposed upon parents, by virtue of their parenthood, in respect of the minor child".[74] It is also important to note that the Convention does not make any specific reference to the issue of the involvement of infants or children in medical research and there are clear limitations from the framework as an authoritative guide to the conduct of infants in research and how it should be carried out.[75] However, the regulation and guidance on the involvement of medical research involving infants may be measured by the

[72] Fortin J. *Children's Rights and the Developing Law* (Cambridge, Cambridge University Press, 2009).
[73] Ng SM and Weindling AM. (2009) 'The impact of network on clinical trials', *Trials*, 10:11.
[74] Feldman D. (ed.) *Civil Liberties and Human Rights in England and Wales* (Oxford, Oxford University Press, 2002), 12.
[75] Consensus on the wording of a provision could not be reached at the drafting stage. See Considerations 1989 Working Group E/CN.4/1989/48, page 70-74 in S. Detrick, et al., *The United Nations Convention on the Rights of the Child: A Guide to the "Travaux Prépatoires"* (Dordrecht, Martinus Nijhoff, 1992). It is important to note that when a child is not competent to give full valid consent, authorization for medical treatment must be obtained from the child's parent.

catalogue of rights within the CRC which can be used as benchmarks. For example, best interests of infants can be negotiated through parents or the family unit, and there are provisions from the CRC to support this theory. Parents are also used as proxy to the decision-making involved in infants' participation in research which will be further explored in the next chapter.

3.2 Good Clinical Practice and European Union Legislation

Good Clinical Practice (GCP) is a European standard governing design, conduct, recording and reporting of clinical trials. The EU is now having an increasing influence on ethical and legal standards in the UK, having introduced harmonised standards in the way of legislative provision coupled with guidance to promote good practice. This therefore imposes a new layer of obligations above and beyond what exists nationally and sits alongside the accompanying international framework. The legal framework in the UK for conducting clinical research was prepared under Directive 2001/20/EC, the European Union Clinical Trials Directive (EUCTD).[76] The EUCTD established specific provisions for the conduct of clinical trials and implementation of the GCP.[77] The EUCTD was later transposed into UK domestic law as the Medicines for Human Use (Clinical Trials) Regulations on the 1st May 2004 (SI 2004/1031). The Medicines for Human Use (Clinical Trials) Amendment Regulations (SI 2006/1928) came into force on 29 August 2006 to incorporate the GCP Directives.[78] The Regulations offer additional protection for a minor - that is, a person under the age of 16 years - who is being considered for a clinical trial but does not cover non-therapeutic research.[79] The Regulations also infer that medicinal trials may be lawfully conducted if "the clinical trial relates directly to a clinical condition from which the minor suffers or is of such a nature that it can only be carried out on minors and some direct benefit for the group of

[76] EU Clinical Trials Directive (2006) at Www.Wctn.Org.Uk/Downloads/Eu_Directive/Directive.Pdf
[77] Good Clinical Practice 2013 at www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/index.htm, accessed April 15th 2013.
[78] UK Medicines for Human Use (Clinical Trials) Regulations at Www.Uk-Legislation.Hmso.Gov.Uk/Si/SI.2004/1031, accessed 3rd January 2013.
[79] EU Clinical Trials Directive (2006) cover only investigations/studies which are undertaken to ascertain the efficacy or safety of a medicine in human subjects. Non-interventional trials or non-therapeutic research are excluded from the Regulations.

patients involved in the clinical trial is to be obtained from that trial".[80] Although there is no precise definition on 'non-therapeutic' research, as discussed earlier, it is often taken to mean research which does not offer any clinical benefit to the research subjects. The provision of the Regulations appears to allow research within its remit to be carried out even if it offers no potential benefit to infants enrolled. There is, however, no reference to the degree of acceptable risk and there is no definition of what 'direct benefit' means within the Regulations.

This comes at a time when more children are expected to be asked to participate in clinical trials as part of an international initiative to provide medicines for children that are fully licensed. The regulations specify that for a minor to participate in a clinical trial, a person with parental responsibility or a legal representative must give informed consent and may withdraw the young person at any time.[81] In the UK, all clinical trials involving medicinal products must now include stringent internal regulation and adhere closely to these guidelines. These changes, which were instituted between 2004 and 2006, were amended and further developed to ensure the integrity of the scientific value of clinical research and its conduct.[82]

The development of the GCP and the extensive amendments caused considerable dissatisfaction in the academic sector. The perception was that the high level of regulation and increased phamacovigilance (that is, drug safety) resulted in increased bureaucracy which has impeded the conduct of a trial. Meeting all the new regulatory requirements was outside the present experience of even experienced triallists. Lack of support for clinical scientists and investigators may be obstacles to starting new trials and encouraging research amongst non-academic clinicians, whose participation and good will is vital to the success of any clinical trial.[83] This is particularly important as a number of triallists have reported the impact of administrative burdens imposed to the EU Clinical Trials Directive resulting in failures of individual trials.[84] Prior to the

[80] UK Medicines for Human Use (Clinical Trials) Regulations 2004, see Regulation 15 and Part 1 of Schedule 4, para 9 and 10).
[81] UK Medicines for Human Use (Clinical Trials) Regulations 2004, see Regulation 15 and Part 1 of Schedule 4).
[82] Ibid.
[83] Ng SM and Weindling M., see n72.
[84] Hanning CD and Rentowl P. (2006) 'Harmful impact of EU clinical trials directive: trial of alerting drug in fibromyalgia has had to be abandoned', *BMJ*, 332(7542):666.

legislation, research involving marketed products and not intended to generate results for marketing authorisation purposes was exempt from these rules.[85] Now, with the current legislation, all research involving humans and any medicinal products is covered by the legislation. Publicly funded research must also fulfil the same requirements as commercially funded research. The sponsors of research studies are responsible for the conduct, design, recording and reporting of the research according to GCP standards.[86]

Prior to 2000, the situation in Europe had not supported paediatric studies. The paucity of paediatric research was recognised by the EU and resolutions and proposals were made in the form of incentives, regulatory and supportive measures in respect of clinical research and development to ensure that new products for children and medicinal products that were already available were fully adapted to the needs of children.[87] There were also requirements that new medicinal and authorised medicinal products, covered by patent or supplementary protection certificates, presented results of studies in children according to an agreed code of practice.[88] The approach towards amendments in 2004 and 2006 were in line with professional and international guidance. However, it is noteworthy that none of the guidelines appear supportive of non-therapeutic research. Yet, multiple trials involving infants and non-therapeutic research are being conducted today and grants continue to be awarded to increase research activity in infants and neonates.[89] For example, I have been involved in assisting in developing the protocol for the TINN study. TINN - *Treat Infections in Neonates* - is a comprehensive drug study evaluating the safety of ciprofloxacin and how it is tolerated by infants. Ciprofloxacin is an antibiotic that has been used for many years in newborn infants and infants less than 3 months old to treat bacteria that are resistant to other antibiotics. Ciprofloxacin is unlicensed for this age group and the European Medicines Agency have prioritised research funding for this drug.[90] The TINN project aims to study pharmacodynamics, safety and side-effects of Ciprofloxacin used to treat infants.

[85] Watson M. (2006) 'Harmful impact of EU clinical trials directive', *BMJ*, 332(7542): 666.
[86] The sponsors are also required to develop a set of operational procedures to cover all areas of research activities and a quality system has to be put in place to ensure record keeping of data from case report forms and is required to capture incidence of adverse events, serious adverse events or unexpected serious adverse reactions from subjects and report these in a timely manner.
[87] MacDonald A, *The Right of the Child: Law and Practice* (Bristol, Jordan Publishing, 2011), 24.
[88] EU Clinical Trials Directive (2006) at Www.Wctn.Org.Uk/Downloads/Eu_Directive/Directive.Pdf
[89] Ibid.
[90] TINN Pharmacokinetics (PK) Study Treat Infections in Neonates (TINN-PK) (2011) ClinicalTrials.gov Identifier: NCT01319435 available at //clinicaltrials.gov/show/NCT01319435.

The research subjects have bloods taken which are anonymised and the dosing effects are studied. It may be argued that although there are no specific benefits to the research subjects who participate, there may be some direct benefit if, for example, safety profiles were determined within the study and dosing were altered for all infants as a result of the study. The TINN study falls within the remit of the Clinical Trials Regulations in as much as medicinal trials may be lawfully conducted if there is some direct benefit for the group of patients involved in the clinical trial.[91] The Medical Research Council (MRC)[92] also stated that "research should only include children where the relevant knowledge cannot by obtained by research in adults" and, further, that non-therapeutic research "is permissible on incompetent children where the children do not object or appear to object in either words or action". This would mean that infants should be allowed to participate in non-therapeutic research that offers them no individual benefit but could benefit future populations as a whole. However, the argument for a utilitarian approach by which the individual's interests is subservient to those of a wider society and used as a means to an end remains controversial.

3.2.1 Charter of Fundamental Rights of the European Union

The role of the EU in promoting ethical research on infants is also referenced in the Charter of Fundamental Rights of the EU.[93] Specifically, Article 1 states that "human dignity is inviolable. It must be respected and protected". Further, Article 3 states that:

> 1. Everyone has the right to respect for his or her physical and mental integrity.
> 2. In the fields of medicine and biology, the following must be respected in particular:

[91] UK Medicines for Human Use (Clinical Trials) Regulations 2004, see Regulation 15 and Part 1 of Schedule 4, para 9 and 10).

[92] Medical Research Council, *Ethics Guide: Research Involving Children* (2004) at www.cardiff.ac.uk/optom/resources/Medical%20research%20involving%20children.pdf , accessed June 2013.

[93] Charter of the Fundamental Rights of the European UN [2010/C 83/02] Note: This Charter has the same legal status as the EU treaties now so states have to comply with it in the implementation of their EU obligations. This is important as it does not create free-standing enforceable rights in the absence of implementing EU legislation.

(a) the free and informed consent of the person concerned, according to the procedures laid down by law;
(b) the prohibition of eugenic practices, in particular those aiming at the selection of persons;
(c) the prohibition on making the human body and its parts as such a source of financial gain;
(d) the prohibition of the reproductive cloning of human beings.

Article 1 and Article 3 are therefore significant as they refer to infants' rights to respect and integrity in the way that any research should be conducted. It also specifically refers to the fields of medicine in that informed consent should be sought, but it does clarify areas where individuals who are non-competent are dependent on their guardians for such protection.

Articles 24 and 35 of the Charter[94] allude to the fact that children have the right to all forms of protection and care for their well-being and that their best interests is of primary consideration in any decisions made. Parents and guardians have the responsibility for their child's best interests and the role of such a principle is to aid those who make decisions for the infants in any area such as research or healthcare. Mnookin and Szwed argued that "what is best for any child or even children in general is often indeterminate and speculative, and requires a highly individualised choice between alternatives".[95] Thus, the best interests test is often criticised as it is believed that, since there is no definition of the principle, or guidance in its application, the values of the particular decision-maker may influence decisions.[96]

It is debatable whether these codes of practice provide adequate and appropriate standards of conduct when transposed to the ethics of conducting research on infants. Although the GCP and global human rights principles contain rather specific statements

[94] In Article 24 Rights of the child refers to "Children shall have the right to such protection and care as is necessary for their well-being. They may express their views freely. Such views shall be taken into consideration on matters which concern them in accordance with their age and maturity, and Article 35 on Healthcare states that "Everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices".
[95] Mnookin R and Szwed E, (eds.) *The Best Interests Syndrome and the Allocation of Power in Child Care*, Providing Civil Justice for Children (London, Providing Civil Justice for Children, 1983), 55.
[96] Ibid.

on how research should be conducted or how consent should be taken, it does not address the specific issues of infants' participation in research and such statements remain too abstract to be able to resolve any specific cases in this category of a population that is vulnerable and non-competent. A pertinent issue is that they cannot be enforced independently, and that they must be integrated into binding law in order to have any real effect. It remains clear that there is a gap in the current international framework which does not address the issues posed by research involving infants.

3.3 Common Law of Negligence

The law of negligence seeks to ensure that as individuals we are responsible for our actions and that we consider those who might be injured by those acts and omissions. The modern law of negligence was established in *Donoghue v Stevenson*.[97] In order to be successful in a negligence claim, the claimant must prove the defendant owed them a duty of care, that the defendant was in breach of that duty, that the breach of duty caused damage and that the damage was not too remote.[98] The duty of care requires health professionals, including researchers, to consider the consequences of any acts and omissions and to ensure that those acts and/or omissions do not give rise to significant foreseeable risks of injury. However there are limitations of the law of negligence as a means of protecting research subjects and providing any guidance for medical researchers. There is a need to prove that damage is caused by negligence and, in the context of research, legally it is difficult to prove that the research intervention and not the subject's underlying condition or illness had 'caused' the harm. The standard of care clinicians are required to meet is known as the *Bolam* test, following the *Bolam* case,[99] which refers to the reasonable opinion of a body of professional men.

[97] Donoghue v Stevenson [1932] AC 562. Mrs Donoghue went to a cafe with a friend. The friend brought her a bottle of ginger beer and an ice cream. The ginger beer came in an opaque bottle so that the contents could not be seen. Mrs Donoghue poured half the contents of the bottle over her ice cream and also drank some from the bottle. After eating part of the ice cream, she then poured the remaining contents of the bottle over the ice cream and a decomposed snail emerged from the bottle. Mrs Donoghue suffered personal injury as a result. She commenced a claim against the manufacturer of the ginger beer.

[98] Ibid.

[99] Bolam v Friern Hospital Management Committee [1957] 1 WLR 582 is an English tort law case that lays down the typical rule for assessing the appropriate standard of reasonable care in negligence cases involving skilled professionals. Case Summary- Mr Bolam was a voluntary patient at a mental health institution run by the Friern Hospital Management Committee. He agreed to undergo electro-convulsive therapy. He was not given any muscle relaxant, and his body was not restrained during the procedure. He flailed about violently before the procedure was stopped, and he suffered some serious injuries, including

The *Bolam* test concludes that if a doctor reaches the standard of a responsible body of medical opinion, he is not negligent. This was later modified by *Bolitho* to indicate a decision must also stand up to logical scrutiny.[100] This case illustrates how the law of negligence has limitations as a framework for regulating research involving infants. The standard of care established in the *Bolam* test has made it notoriously difficult for claimants to succeed in negligence claims.[99] However, we can transpose these principles into research conduct in infants such that all researchers and doctors have a duty of care to fully inform parents of any possible risk of harm when enrolling their infants into research.[101] In fact, at one time, it was regarded as giving the medical profession something close to immunity but the *Bolitho* modification has changed this. A claim in negligence is only available where there is damage, but there are very few if any cases[102] which deal specifically with the standards of care applicable to a clinical researcher such that the guidance offered by the tort of negligence is at a very abstract level.

3.4 Mental Capacity Act

Prior to the Mental Capacity Act (MCA) 2005, any physical intervention without the consent of the adult was lawful only if it was in the person's best interests. In *Re F*,

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fractures of the acetabula. He sued the Committee for compensation. He argued they were negligent for not issuing relaxants, not restraining him and not warning him about the risks involved.

[100] Bolitho v City and Hackney Health Authority [1997] 4 All ER 771. The claimant's son was admitted into the hospital for respiratory difficulties and was placed under the care of Doctor Horn. Doctor Horn did not see the patient when the nurse had called her, and on a second occasion, the doctor delegated the care to another doctor, her junior, Doctor Rodger. This doctor also did not see the claimant's son. This led to further complications in the patient and then severe brain damage from which he eventually died. The defendants argued based on the Bolam v Friern Hospital Management Committee case that their decision not to have intubated him earlier could be confirmed by a reliable and respectable body of opinion.

[101] Both Bolam and Bolitho's case concern the standard of care when it has been alleged that the doctor was negligent in the treatment given or not given to the patient. In Sidaway v Bethlem Royal Hospital [1985] AC 871, C had an operation performed where there was an inherently small 2% risk that it could lead to spinal damage, even if the surgery was performed properly. C ended up severely disabled as a result of complications of the surgery and sued the hospital and deceased surgeon. The surgeon told C that there was a chance of disturbing the nerve during the surgery but did not disclose the small risk about the possibility of damage to her spinal cord. However, the Court found that the hospital and surgeon were not liable to pay for personal injury caused to Ms Sidaway since she had not proved on the evidence that the surgeon had been in breach of duty by failing to warn her of that risk.

[102] In Wilsher v Essex Area Health Authority [1986] 3 All ER 801, 812: "Where the doctor embarks on a form of treatment which is still comparatively untried, with techniques and safeguards which are still in the course of development, or where the treatment is of particular technical difficulty, if the decision to embark on the treatment at all was justifiable and was taken with the informed consent of the patient, the court should in my judgment, be particularly careful not to impute negligence simply because something has gone wrong" (*per* Mustill LJ). This case provides some detail on how the courts might approach the standard of care required of a researcher working at the frontier of knowledge.

the courts authorised full sterilisation to be performed on a severely mentally disabled woman who had sexual relationships with a fellow patient as there were concerns that she would not be able to cope with a pregnancy.[103] The procedure was declared to be lawful on the grounds that it was in her best interests. The principle of best interests applied in this case persists, but it now has a statutory status.[104]

The MCA provides a statutory framework for people who may not be able to make their own decisions because of, for example, learning difficulties, brain injury or mental health problems. The Act sets out who can take decisions, in which situations, and how they should go about this.[105] However, the MCA is relevant only to research involving adults over the age of 16[106] in England and Wales, except Clinical Trials of Investigational Medicinal Products (CTIMPs)[107] and provides the legal arrangements to enable adults lacking capacity to consent to take part in therapeutic research other than CTIMPs (including health and social care research) that would otherwise require the participant's consent. The MCA regulates research on those lacking capacity but it cannot be applied to research on children.[108] Nevertheless, presumably the courts would refer in part to the principles of the MCA in any given dispute about research involving children and infants who also lack capacity, therefore it is useful to examine how the MCA bears on the issue of whether non-therapeutic research on infants could be lawful.

The legality of non-therapeutic research involving adults, although widely supported by research communities and by medical advisory colleges, remains uncertain. The MCA clarifies and supplements the common law in relation to research involving those who are over 16 and who lack capacity. However, it does not clearly distinguish between therapeutic and non-therapeutic research and the Act remains limited in its scope and does not apply to the testing of new drugs.[109] None of the

[103] Re F (Mental patient sterilisation) [1990] 2 AC 1.
[104] See Mental Capacity Act 2005, section 4.
[105] See Appendix.
[106] The MCA Act section 2(5) states that the Act does not authorise powers to be exercisable in respect of under 16s and therefore the MCA does not apply to children younger than 16 who do not have capacity.
[107] The Medicines for Human Use (Clinical Trials) Regulations 2004 make legal provision for participation in CTIMPs by adults lacking capacity to consent.
[108] In the MCA sections 30-33, the Act provide lawful authority for research to be carried out in adults (16 years and older) without capacity provided that the research has been approved by an appropriate body.
[109] In the MCA Sections 30-33 of the Act provide lawful authority for intrusive research to be carried out. Under Section 30 of the Act, research is intrusive if it is of a kind that would be unlawful if it was carried

current legislative frameworks refers specifically to infants and this is an area that remains uncertain, particularly in the area of non-therapeutic research. The MCA section 31(5) states that the research must have the potential to benefit the research subject without imposing a disproportionate burden and it must be intended to provide insight into the treatment, care or causes of the condition which the research subject is affected by. In section 31(6) the Act also states that any research that falls within the remit of section 31(5), there must be reasonable grounds to believe that anything done to the research subject must not be unduly invasive or restrictive.[110]

If the MCA's principles are applied to the issue of whether we could conduct research involving infants and children who lack capacity, we can infer that research can also be conducted in infants who lack capacity even if the research does not directly benefit the infants but may be connected to the condition the infants may be suffering as long as it is not unduly invasive. It can be further extrapolated that all forms of consent lie with the parents or guardians, relying on parental responsibilities and their judgement to make a decision on whether or not to consent to their infant's involvement in research.

None of the regulatory frameworks, principles or guidance described can be specifically related to the conduct of research involving infants and huge gaps in the guidance, knowledge and perspectives are noted. It remains controversial as to whether infants are justified in their participation to research for the benefit of the greater good if there is no direct benefit to the individual infant. It is further argued with the increasing number of research studies involving infants, should infants be protected from the inevitable discomfort and risks from blood samplings when recruited into clinical trials and how can this be regulated?[111] If the overarching principle lies in that the interests of

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out "on or in relation to a person who had capacity to consent to it, but without this consent". Therefore intrusive research means research that would legally require consent if it involved people with capacity. Intrusive research is not limited to trials of clinical interventions. It includes non-interventional research where consent is legally required, for example involving the processing of personal data or the administration of questionnaires, interviews or observations. Under Section 30 of the MCA, clinical trials of investigative medicinal products are specifically excluded from the research provisions of the Act. This is because separate provision is made for including adults lacking capacity in Schedule 1 of the Medicines for Human Use (Clinical Trials) Regulations 2004.

[110] MCA Sections 31(5) and 31 (6).

[111] UK Medicines for Human Use (Clinical Trials) Regulations at Www.Uk-Legislation.Hmso.Gov.Uk/Si/SI.2004/1031, accessed 3rd January 2013.

the infant must prevail over all other interests of science and society, then any non-therapeutic research involving infants should be challenged. However, research with adults cannot simply be generalised or extrapolated to infants and this chapter has argued that there is a niche required for research in the infants' population that is essential. The current body of law that has been described thus far remains underdeveloped with regards to research involving infants. The implications of the Medicines for Human Use (Clinical Trials) Regulations 2004 which requires proof of a 'direct positive benefit test'[112] is considered unduly restrictive of some types of paediatric research which are non-therapeutic as discussed previously in Chapter 2. Cave argues that although children's rights must be safeguarded, research must be encouraged in rare paediatric conditions where it cannot be conducted in adults.[113] She also states that the law, which should provide a minimum standard of protection for both children's rights and interests *and* society's interest in the furtherance of research, is at times vague and contradictory.[114] Research however, has enabled major improvements in fetal diagnosis and medical care to improve the survival of extremely premature infants born at the cusps of viability. In the next section, the ethical, legal and social issues within the context of critical care given to extremely premature infants born before 26 weeks' gestation is discussed.

3.5 Nuffield Council Critical Care Decisions in Fetal and Neonatal Medicine

Improved neonatal survival is a result of advancement in the delivery of intensive care given to extremely premature infants. The Nuffield Council on Bioethics developed a working party to establish a report which examines the ethical, social and legal issues that are related to critical care decision making in fetal and neonatal medicine.**[115]** It proposes to offer guidance on decisions of whether a premature infant should be resuscitated or not at birth, whether further treatment should be instituted, withheld or continued after birth, and such decisions will undoubtedly affect whether the infant lives or dies.

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[112] Ibid., see Schedule 1, part 4.
[113] Cave E. (2010) 'Seen but not heard: children in clinical trials', *Medical Law Review*, 18(1): 1-27.
[114] Ibid.
[115] Nuffield Council on Bioethics (2006) 'Nuffield Council Critical Care Decisions in Fetal and Neonatal Medicine', *http://nuffieldbioethics.org/wp-content/uploads/2014/07/CCD-web-version-22-June-07-updated.pdf*

The best interests principle is central to medical practice and the Working Party concluded that the best interests of a baby must be a central consideration in determining whether and how to treat him or her.[116] However, it does not appear to consider that the baby's interests should invariably take precedence over the interests of these other parties and it is the Working Party's view that those who make decisions in respect of an infant must also consider the interests of others who may be affected by such decisions such as other family members.[117] In the case of baby Elliot discussed within the report, who was born at 41 weeks with severe brain injuries, was unresponsive and ventilator-dependent, the medical teams were in agreement that further life support was not justified when the prognosis was so poor. However, the parents believed life was sacred and did not agree to withdrawal of care. Elliot died later of severe infection three months later. Although health professionals chose not to challenge the parents, this case could have been brought to court to determine whether Elliot gained any benefit to life and experienced any meaningful human interaction in his limited life, what were the burdens to his treatment and whether he was he subject to pain and distress.[118] In reviewing the current legal principles in the UK, is the current model of decision making that allows doctors and parents broad discretion to determine an infant's fate sufficiently sensitive to his or her best interests? It has been acknowledged by the Working Party that there were real difficulties in knowing what is best for an infant within the context of decision making on whether to initiate, withhold or withdraw treatment. Parents have interests that are distinct from those of their baby, and health professionals may also have interests that may conflict with their ability to represent the best interests of the infant, but the principles of best interests of the infant should remain a central one in decision making about the infant and it carries the greatest weight. The infant's interest in living or dying, or in avoiding an 'intolerable' life is more important than the interests that others may have in any significant decisions made about him or her.[119]

It is clear that although ethical guidance currently exists in fetal and neonatal critical care decision making, it remains vague and there is still varying degrees of

[116] Ibid, page 14
[117] Ibid, page 17
[118] Ibid, page 101
[119] Ibid, page 159

consistency in relation to decisions related to treatment withdrawal and views on quality of life. In relation to the ethics of imparting clinical research, whether it is therapeutic or non-therapeutic, there is currently no emphasis in this Nuffield guidance on the practice of research in these infants. Research ethics committees thus face a difficult task balancing the relevant ethical factors, as is discussed in the next section.

3.6 Research Ethics Committees

In the UK, it is against the law, under the Medicines for Human Use (Clinical Trials) Regulations 2004, to start, recruit for or conduct a clinical trial of an investigational medicinal product until there is a favourable opinion from a recognised "Research Ethics Committee".[120] The role of ethics committees is to provide protection assurance to the public by reviewing in detail the research protocols, the aims and objectives, the suitability of investigators, the methodology and materials used, the documentation and consent procedures and ensuring that the overall research conducted is in accordance to GCP standards. Their responsibility is to ensure that the research participants' rights, well-being and safety are assured when participating in any research.[121] The ethics committee are also responsible for providing either a favourable or unfavourable decision on the research study. The Research Ethics Committee (REC) undertakes the ethical review process of an application. The research application for ethical review must be made by the Chief Investigator for the research study.[122] Research networks were also developed to support and coordinate high quality clinical research and to facilitate the conduct of research and other studies within the National Health Service (NHS).[123] The National Institute for Health Research (NIHR) Comprehensive Clinical Research Network (CCRN) was created in the UK as part of the government's research and development strategy so named as *Best Research for Best Health* to provide a world-class infrastructure for clinical trials in all areas of disease and clinical need within the NHS. The NIHR CCRN works together with the six

[120] UK Medicines for Human Use (Clinical Trials) Regulations at Www.Uk-Legislation.Hmso.Gov.Uk/Si/SI.2004/1031, accessed 3rd January 2013.
[121] NHS Research Ethics Service (2009) at *//www.nresform.org.uk/AppForm/display/login.asp?b=1* [hereinafter "NHS Research Ethics Service"].
[122] "NHS Research Ethics Service".
[123] UK Clinical Research Network at *//www.ukcrn.org.uk/index.html*, accessed 1 May 2013 [hereinafter "UK Clinical Research Network"].

Topic Specific CCRNs and a Primary Care Research Network to support a national portfolio of clinical trials and other studies. The Medicines for Children Research Network (MCRN) was established in 2006 to improve the clinical research environment for children with a stated aim "to facilitate the conduct of randomised prospective trials and other well-designed studies of medicines for children, including those for prevention, diagnosis and treatment".[124] A similar function is provided by CRN for other patient groups. If a trial involves an unlicensed medicine without the support of a pharmaceutical company, then a significant amount of funding and resources are required to conduct such a trial. There needs to be intensive input from NHS trusts or organisation pharmacists and the Research and Development departments to deal with manufacturing the investigational medicinal product (IMP), ensuring there is good quality control, assessor-blinding and appropriate dispensing of the treatment or placebo intervention.[125] This requires considerable funding, resources and specialist input towards the trial conduct. In addition, a clinical therapeutic investigative or medicinal trial requires sponsors which are usually a university or an NHS trust who are solely responsible for the trial's conduct, recording and reporting of adverse effects and design of the trial.[126] Many UK research centres, professional associations and organisations also issue their own codes of conduct for good practice. While some set stringent criteria, others may have more general views and provide guidelines for codes of conduct rather than set absolute standards.

An interesting example was a randomised controlled trial BOOST-II UK trial[127] where extremely premature infants born below 28 weeks were randomly divided into two groups. In one group the aim was to keep the oxygen saturation level as much as possible in the range 85-89% and in the other group in the range 91-95%. The initial aim of the trial was to recruit 1200 infants but an interim analysis conducted showed that infants who were having their oxygen in the range 91-95% were surviving more often than those who were having their oxygen targeted in the range 85-89%. The research ethics committees and data monitoring committees asked for the trial to be stopped before the full recruitment target was reached as the difference between the 2 groups was so clear indicating a much higher risk of death in infants randomised to the lower

[124] Medicines for Children Research Network at *//mcrn.org.uk/*, accessed 12th January 2013.
[125] UK Clinical Research Network.
[126] Ibid.
[127] BOOST II UK trial Benefits of Oxygen Saturation Targetting at https://www.npeu.ox.ac.uk/boost

oxygen saturation range. One question that arises from this trial is whether research ethics committees should bear some responsibility as well as the medical profession, in failing to foresee such an unexpected trial result, and in turn for wrongfully randomising babies to receive oxygen within the accepted standard-of-care limits.

In the context of research involving infants, the development of research ethics committees and research networks such as the MCRN was aimed at facilitating research in children and infants in the UK. It could be said that they constitute a breach in the legal principle of protectionism of the infant. None of these committees or networks appear to have any legal binding to the law of best interests or rights to the infant that will be discussed in the next section.[128] Yet, the current research guidelines in the UK promotes a view which is contrary to the individualised infants' best interests principle because there is a greater good at stake and infants need to be involved and not excluded from research.[129]

3.7 Royal College of Paediatrics and Child Health Guidance

In 2000, the Royal College of Paediatrics and Child Health (RCPCH) in the UK published guidance which indicates that research procedures that are not intended to directly benefit the child may not be necessarily either unethical or illegal.[130] The guidelines stated that they were written for everyone involved in the planning, review, and conduct of research with children. The RCPCH's first guidelines - then the British Paediatric Association - were published in 1980. Since then, there has been significant progress in the understanding of children's interests, in legal requirements, and in the proper regulation of research. The revised guidelines take account of such developments and were based on the following principles:[131]

> (1) Research involving children is important for the benefit of all children and should be supported, encouraged and conducted in an ethical manner;

[128] Brazier M and Cave, E. *Medicine, Patients and The Law* (London, Penguin, 2007). Although the Clinical Trials Regulations in the UK require that trials that fall within its remit must have ethical approval, for research that falls outside the remit of the CTA there is no legal requirement for ethics approval.
[129] Ibid.
[130] Child Health: Ethics Advisory Committee Royal College of Paediatrics (2000) 'Guidelines for the ethical conduct of medical research involving children', *Archives of Disease in Childhood*, 82(2): 177-82.
[131] Ibid.

(2) Children are not small adults, and a child or infant has additional, unique set of interests;
(3) Research should only be done on children if comparable research on adults could not answer the same question;
(4) A research procedure which is not intended directly to benefit the child subject is not necessarily either unethical or illegal;
(5) All proposals involving medical research on children should be submitted to a research ethics committee; and
(6) Consent should be obtained from the child, parent or guardian as appropriate. When parental consent is obtained, the agreement of school age children who take part in research should also be requested by researchers.

The RCPCH goes on to state that:

Children are unique as a research group for many reasons. They are the only people, in British law, on whose behalf other individuals may consent to medical procedures. Many children are vulnerable, easily bewildered and frightened, and unable to express their needs or defend their interests.[132]

Potentially with many decades ahead of them, they are likely to experience, in their development and education, the most lasting benefits or harms from research. The RCPCH also contends that:

It was important to validate in children the beneficial results of research conducted in adults and that research with children is worthwhile if each project has an identifiable prospect of benefit to the child; is well designed and well conducted in its protocol; does not simply duplicate earlier work that has been published; is not undertaken primarily for financial or professional advantage; involves a statistically appropriate number of subjects and eventually is to be properly reported.

[132] Ibid.

The RCPCH provide the closest guidance we have on research involving infants and expressly stipulates that research can be undertaken as long as it not "against the infants' best interest".

3.8 Concluding Remarks

The current legal and ethical framework and regulations governing therapeutic and non-therapeutic research involving infants remains vague, particularly with regard to protection of infants in clinical trials and within the area of non-therapeutic research which is an area of greatest contention concerning the infant. The law apparently does not appear to allow non-therapeutic research involving infants as the term non-therapeutic research refers to research which confers no personal benefit to the infants and the overreaching principle is that the interests of the child must prevail over the interests of science and society. Should the law therefore be more explicit in its guidance and direction of what confers personal benefit when research is being undertaken? A gulf exists between what is legal and what is practised with research involving infants currently being promoted and conducted regardless of the law. Indeed, even the RCPCH available guidelines - that state "a research procedure which is not intended directly to benefit the child subject is not necessarily either unethical or illegal" - are not consistent with the legal principle of best interests and, therefore, cannot be applied to infants as the law still upholds the fundamental principle that if research were not intended to benefit the infant, then it can be considered unethical. In the absence of any clear legal and ethical guidance, it is felt that any authorisation would not be deemed to be in the infant's best interests to be engaged in any research participation where he or she does not stand to gain anything personally from it. Where the courts have been asked to assess whether such proposed interventions are within the child's best interests, they generally do not consider the wider interests of those caring for the child or the wider interests of society. The RCPCH took the view that provided research cannot be carried out in adults and an appropriate risk to benefit assessment has been undertaken with minimal risk and minimal harm towards the child, non-therapeutic research that does not necessarily benefit the infant can be deemed ethical.[133] Whether the RCPCH, as an advisory body, can make such a claim as it merely acts as an expert

[133] Ibid.

organisation remains arguable. There may be an ethical argument that may be mounted to support this contention to allow it to be permissible to conduct non-therapeutic research involving infants - indeed, the Clinical Trials Regulation do authorise non-therapeutic medicinal trials involving infants subject to strict conditions[134] - yet it remains unclear whether non-therapeutic research in children beyond medicinal products such as psychology or surgery interventions would be lawful. Furthermore, it appears to contradict what had been previously described within the global/international principles of human rights from the CRC, and the law is still unclear. There has been no case law to date to render such non-therapeutic research as lawful nor has it been proven as ethically justifiable. Arguably, where there is serious concern that risk may be more than minimal, the courts in any future case law - and in light of statutory prohibition of non-therapeutic research - may well be influenced such that approval will be less likely to be given compared to therapeutic clinical research. Quite clearly, there is a paucity of clear guidelines within the legal and ethical framework on the issue specific to infants and research. The next chapter seeks to examine how we can justify research involving infants based on the argument that parents have a right and responsibility to make such judgements when risks are minimal or negligible.

[134] UK Medicines for Human Use (Clinical Trials) Regulations 2004, see Regulation 15 and Part 1 of Schedule 4, para 9 and 10).

CHAPTER 4: PARENTAL RIGHTS, RESPONSIBILITY AND WHAT IS ACCEPTABLE RISK?

This chapter examines the crucial issues related to how parental rights and responsibilities can be defined in the context of recruitment into clinical research. It provides a critical analysis of the issue of risk exposure when participating in research that has no direct benefit and then moves to consider the difficulties faced in pinning down what is acceptable risk in research. It will be argued that leaving decisions pertaining to research participation for infants to parental discretion is the only sensible solution.

4.1 Parental Rights and Responsibilities

The term 'parental rights' has found recent disfavour within the children's rights debate as such rights that exist are certainly not absolute, and this applies especially in the case of rights to consent or involve one's child in research. Such a right must be exercised 'responsibly' in the best interests of the child. However, this does not mean that parents do not have any rights as in most jurisdictions the parents or guardians have legally recognised and enforceable rights of custody, and other rights that come with the recognition of a family life that will enable them to carry out their parental duties.[135] 'Parental responsibility' is a term used to describe the legal duty that a parent has to their child.[136] Having parental responsibility gives rise to the right to contribute to decision making regarding a child's future and any decisions affecting their future too. For example, the parent has responsibilities towards their children in the area of their general upbringing, naming the child, providing a home for the child, deciding on their religious upbringing, choosing and providing the child's education, deciding on where the child goes to school, and making different decisions about their child's health, education, and their physical and emotional welfare. This responsibility includes agreeing to the child's medical treatment, allowing confidential information about the

[135] Children's Act 1989, section 3(1).
[136] Ibid. In this Act "parental responsibility" means all the rights, duties, powers, responsibilities and authority which by law a parent of a child has in relation to the child and his property.

child to be disclosed and being able to give consent regarding medical treatment and participation in research.[137]

In addition to the court's statutory powers under the Children's Act, the courts also have an inherent jurisdiction which enables them to make orders and decisions in respect of the child. The *parens patriae* jurisdiction has been described as an ancient prerogative jurisdiction of the Crown which had been delegated to the courts to protect the persons and properties of those who were unable to do so themselves.[138] Thus, in dealing with children, the court acts in its *parens patriae* capacity in promoting and protecting the interests of the child in relation to medical treatment. In principle, the court may consider any case concerning an incompetent child under this jurisdiction. Although wardship was historically used as a procedure to exercise the court's inherent jurisdiction, it is now rarely undertaken in medical treatment cases, except in the event of a dispute over a proposed course of treatment or in the absence of lawful authority to proceed, the courts may seek to use the inherent jurisdiction by which the courts' paramount consideration must be that of the best interests of the child.[139] The best interests principle seems to demand that there is only one solution after evaluating the harms and benefits to the intervention. However, a range of factors may be taken into account in establishing that the best interests option may be variable and that opinions may differ in establishing the evidence needed to determine them and the weight that should be given to competing factors. No matter how simply a proposition such as this is made, applying it in practice is not an easy task as any departure from the best interests consideration may be seen as lessening the importance of the child's best interests. In the end, much discretion will lie with the courts as to how much and what factors the court is permitted to take into consideration, how it chooses to take it into account and how those factors are weighed up in the balance.

4.2 Grimes v Kennedy Krieger Institute Inc

[137] Ibid.
[138] Seymour, J. (1994) 'Parens patriae and wardship powers: their nature and origin', *Oxford Journal of Legal Studies*, 14: 159-199.
[139] *Re Z* (minor) (freedom of publication) [1995] 4 All ER 961, CA at 986 per Bingham MR and Re J (a minor) (Wardship: Medical treatment) [1990] 3 All ER 145, CA per Taylor LJ.

There remains a paucity of examples of court judgements in the UK related to research protection policies in children. Although US cases have no direct bearing on legislation in the EU, one illustrative example may be taken from the landmark case of *Grimes v Kennedy Krieger Institute Inc* (KKI)[140] in the US where, for the first time, a court had addressed the issue of parental rights and authority in being able to consent to their children becoming research subjects, especially when the research is non-therapeutic and offers no direct benefit to the child whilst imposing minimal risk. The court addressed the relationships of researchers and institutions that conduct non-therapeutic research towards child subjects and further challenged the notion of acceptable levels of risk in paediatric research where the research participants gain no direct benefit.[141] There were two negligence cases in which the claimants were young children recruited into non-therapeutic research aimed at determining the safety and effectiveness of different methods of lead paint abatement. The case involved allegations that children were put at significant risk of being exposed to lead poisoning as a result of participating in the research. The claimants alleged that KKI had arranged for some houses in the research study to have only partial lead paint abatement and had encouraged families with young children to stay in these houses while the children who were research subjects had their bloods sampled over time. It was also alleged that KKI was aware that one of the children's blood samples showed a dangerously high blood lead level and KKI failed to notify the parents in a timely manner. It was also alleged that KKI did not fully provide the parents with a clear and full explanation of the research. Only children who were from low income households appeared to have been recruited as subjects in the research and questions were raised of whether parents were enticed by money or other items offered by KKI. The trial court granted KKI motion for summary judgment and finally dismissed the case, basing the judgment on the grounds that the KKI researchers do not have a legal duty to warn claimants of the presence of lead dust. The claimants appealed, stating that the court's decision was incorrect and that it was a matter of law that any institution conducting non-therapeutic research must have a duty to warn any participant's parent or guardian of his/her legal right to be aware of the dangers involved in any research undertaken, especially if the researcher

[140] *Grimes v Kennedy Krieger Institute Inc*, 366 Md 29;782 A2d 807 Mdlexis 496," ed. Accessed 8th April 2013 http://www.courts.state.md.us/opinions/coa/2001/12800pdf.[herinafter Grimes v Kennedy Krieger Institute Inc].
[141] Ibid.

has any knowledge of the potential harm towards the research participant and he/she is unaware of the danger.[142] Research communities feared that as a result all forms of public health research involving minors would be halted.[143]

The Court of Appeal later reversed the trial court's ruling stating that the very nature of non-therapeutic scientific research on human subjects can and will normally create special relationships between researchers and recruits out of which duties arise. The court indicated that 'acceptable risk' was indicted in the context of the case as including "minimal risk".[144] It described the legal theories that could delineate the obligations of non-therapeutic researchers such as contractual obligations. The court held that contractual obligations exist as researchers and subjects entered an agreement within the consent procedures and that the consent form creates a legally binding agreement.[145] The court specifically reserved judgement on whether contractual obligations are created in non-therapeutic research. The court also held that regulatory obligations were in place to provide a means of ensuring subjects' rights. Moreover it was noted that:

> In the court's view, the health of the children should not be subjects of non-therapeutic research which has the potential to be harmful to the child. It is, first and foremost, the responsibility of the researcher and the research entity to see the harmlessness of such non-therapeutic research, and consent from the parent or guardian can never relieve the researcher of this duty.[146]

The court also held that there should be restrictions to parental rights and authority to consent to their children's participation of non-therapeutic research after noting that children are not equivalent to rats, hamsters and monkeys used in research. The court further stated that "parents are duty-bound to act in their children's best interests and that it not in the best interests of healthy children to be intentionally put at

[142] Grimes v Kennedy Krieger Institute Inc, 366 Md 29;782 A2d 807 Mdlexis 496.
[143] Pelton T. (2001) 'Two universities, Krieger Institute seek reconsideration of lead paint opinion', - *Baltimore Sun*, 3B.
[144] Mastroianni A and Kahn JP. (2002) 'Risk and responsibility: ethics, *Grimes v Kennedy Krieger*, and public health research involving children', *Am J of Public Health*, 92: 1073-9.
[145] Pearce M. (2002) 'Children as subjects in non-therapeutic research: Grimes v Kennedy Krieger Institute Inc.', *Journal of Legal Medicine*, 23: 423.
[146] See n135.

risk in non-therapeutic research where his/her health may be impaired in order to test methods that may be beneficial to all children in the future".[147] The argument from the defence was that the children as participants had, in fact, benefited in the study because if they had not moved into the research homes they might have ended up in other similar contaminated homes that were receiving no treatments.[148]

The *Grimes* case remains the only US landmark court case to explicitly address and argue that it was unethical to recruit children into non-beneficial research that offered subjects a "negative" risk/benefit profile.[149] It raised legal and ethical issues related to the enrolment of children in non-therapeutic research projects that may present a risk of harm and no possibility of direct benefit to the individual child subjects. It also appeared to impose a requirement that all non-therapeutic research should be harmless and that any risk of harm must be conveyed by researchers and institutions to the subjects or their parents/guardians where the subjects are minors. The restrictiveness of this case caused concern to many research communities and institutions such as KKI because public health research that compares how effective a preventative intervention is in children is widely conducted in the public health sector. The "no-risk" standard imposed is considerably stricter than the accepted research regulations which permit research that presents with "minimal risk".[150] The Court of Appeals reversed the trial court's ruling that institutions and research communities do not have any obligation or duty to fully inform and protect research subjects. It was also correct in its ruling that there should be a very cautious approach toward non-therapeutic research in non-competent subjects such as children and there are ethical obligations not to exploit research subjects.[151]

The court's adoption of a "no risk" standard in *Grimes* resulted in many academic organisations requesting reconsideration of its ruling, arguing that such a

[147] Ibid.
[148] Glantz L**.** (2002) 'Nontherapeutic research with children: Grimes v Kennedy Krieger Institute', *.Am J Public Health*, 92:1070-3.
[149] Wendler D. (2004) 'Risk standards for pediatric research: rethinking the *Grimes* ruling. Kennedy Inst', *Ethics Journal*. 14(2):187-198.
[150] US Department of Health and Human Services, *Children Involved as Subjects in Research: Guidance on the Hhs 45 Cfr 46.407* (2005), 429.
[151] Glantz L. (2002) 'Non therapeutic research with children: Grimes v Kennedy Krieger Institute', *Am J Public Health*, 92:1070-3.

standard would prohibit any future important research. However, the court denied any motion for reconsideration and attempted to clarify its position: "by the term 'any risk', we meant that any articulable risk beyond the minimal kind of risk that is inherent in any endeavour". The statement relates to non-therapeutic research studies which have no direct medical benefit to the child or research subject whatsoever, so any balance between risk and benefit is necessarily negative.[152] To reconcile the statement of the court above, it would appear that the court seems to permit some minimal risk but it also seems to convey that any risk is too great in the context of non-therapeutic research in children. One of the most important issues is whether it is ethical to withhold effective public health and environmental interventions from research subjects in order to satisfy scientific goals which may benefit future populations.[153]

4.3 What is Acceptable Risk?

The problem we face is the issue of identifying what is 'acceptable risk', and what type of risk in non-therapeutic research may children be ethically or legally exposed to? Is there a level of acceptable risk to which we can justifiably expose infants to in the pursuit of non-therapeutic research? In 1996, an appellate court in New York heard a similar case - *TD v NY* - regarding non-therapeutic research involving incompetent research subjects.[154] In that case, the claimants brought action to challenge the US regulations of the New York Department of Mental Health that sanctioned exposure to greater than minimal risk in non-therapeutic experiments on adults who lack capacity and on children. The court noted that "a parent or guardian may not consent to have a child or subject submitted to painful or potentially life threatening research procedures that hold no prospect of any benefit to the child and may have the same result as a denial of necessary medical treatment". The claimant's arguments had never been proven in this case as the trial court dismissed the case before a trial was upheld.[155]

[152] Grimes v Kennedy Krieger Institute Inc, 366 Md 29;782 A2d 807 Mdlexis 496.
[153] Buchanan D and Miller F. (2006) 'Justice and fairness in the Kennedy Krieger Institute lead paint study: the ethics of public health research on less expensive, less effective interventions', *American Journal of Public Health*, 96: 781-7.
[154] TD v NY State Office of Mental Health, 228 Ad 2d 95,650 Nys 2d 173 (1996) Rev on Other Grounds 690 Ne2d 1259 (1997).
[155] Ibid.

The *KKI* case and the *TD* case were criticised as appearing to prohibit any non-therapeutic research from being conducted in children and infants. The courts did not resolve the ethical debate on whether such research involving infants may continue or be abolished altogether. It may be acceptable to say that parents should not submit their infant to harmful research procedures that offers no direct benefit to the infant. However, the prohibition of the court on any form of "painful" procedures may seem to prohibit even the act of drawing blood. This would be perceived as halting any meaningful research involving blood sampling.[156] The US research regulations defined 'minimal risk' as any situation where the probability and the magnitude of harm or discomfort endured or anticipated in the context of research are not therefore greater in and of themselves compared to those ordinarily encountered in the *daily life* or during a performance of a routine physical and psychological examination or test.[157] The reference to *daily life* raises the question of whose daily life is to be used as a reference point. Daily lives of inner city populations are likely to be riskier than those compared to suburban populations, and the literal application of such a regulation would appear to allow 'riskier' research within the inner city compared to the suburbs. In further exploring how we can quantify the notion of acceptable risk or harm in the context of research, the chapter will now discuss the evidence related to perceptions of pain and assessments of risk.

4.3.1 Perceptions of Pain and Assessment of Risk

There is strong evidence of a difference in age perception of pain and a difference between older children's and infants' perception of pain.[158] A differential tolerance of pain appears to increase with age and maturity when the child no longer perceives medical interventions as punitive.[159] A child's or an infant's response may be unpredictable and varied and may alter as they mature and develop, such that current generalisations and guidance on risks do not apply. One procedure may not bother one

[156] Kopelman L. (2002) 'Paediatric research regulations under legal scrutiny: Grimes narrows their interpretation', *J Law Med* Ethics, 30: 38-49.
[157] US Department of Health and Human Services, "Children Involved as Subjects in Research", Guidance on the HHS 45 Cfr 46.407 Review Process
http://www.hhs.gov/ohrp/policy/populations/guidance_407process.html Accessed March 30th 2013.
[158] Gibson SJ and Farrell M. (2004) 'A review of age differences in the neurophysiology of nociception and the perceptual experience of pain', *Clin J Pain*, 2(4): 227-39.
[159] Haslam D. (1969) 'Age of perception of pain', *Psychological Science*, 15: 86-87.

infant, but may be distressing to another. The UK's RCPCH[160] recommended that assessment of any potential risk or harm should include estimates of types of intervention described in the research protocol such as: (1) how invasive or intrusive the research could be towards the participant and how severe may the harms associated with research procedures likely to be; (2) what are the probabilities of these harms occurring during the research period; (3) might any adverse effects be either short or long lasting, or may it be immediate or not evident until years later; (4) whether matters of equity are taken into account such as are a few children drawn into too many projects simply because they are available or are researchers relying unduly on children who already have many problems?; and (5) if evidence of harm in giving or withholding certain treatment emerges during the trial, how will possible conflict between the interests of the child subjects and of valid research be managed and will there be interim analyses performed to ensure any potential risks are identified. Assessments of any risks of potential harm should include a review estimate by the researcher as some potential harm may not be obvious without careful consideration of their consequences. For instance, in non-therapeutic research related to investigations into inherited genetic disorders that may present in adult life, while it is asymptomatic in a child or infant and it may be beneficial, there is a risk that it may also have very harmful effects from a psychological aspect knowing that one has an inherited genetic condition that may deteriorate in future years, and may affect the child's opportunities and their freedom of choice. The RCPCH states that risk may be categorised as minimal, low or high whilst taking into account social and emotional effects. These are defined as: (a) *minimal or the least possible risk* where any research procedures defined as questioning, observations, recording and measuring children, provided that such procedures are carried out in a sensitive way, and that consent has been given. Examples of procedures with minimal risk include collecting a single urine sample or obtaining blood from a sample that has been taken as part of treatment; (b) *low risk* describes any research procedures that may cause brief pain or tenderness, and may cause small bruises or scars. Many children fear needles and for them low rather than minimal risks are often incurred by injections and venepuncture; and (c) *high risk* describes any research procedures such as organ biopsies (for example, lung or liver biopsy, arterial puncture,

[160] RCPCH (2000) 'Guidelines for the ethical conduct of medical research involving children', *Archive of Disease in Childhood*, 82(1): 178-82.

and cardiac catheterisation) that are not justified for research purposes alone. These procedures should be carried out only when research is combined with diagnosis or treatment intended to benefit the child concerned.[161]

It is therefore viewed by the research communities that any research that subjects children or infants to anything more than minimal risk - defined by the RCPCH above - should be subject to serious ethical review. For example, according to the RCPCH,[162] procedures such as blood samplings are very common and whilst an infant cannot give consent by reason of immaturity of non-competence, their parents and guardian may consent to such research procedures for non-therapeutic research as long as it carries a minimal risk and as long as the parent or guardian has sufficient informed consent and had been given a full explanation and understands the full extent of the research protocols. Many older children fear the venepuncture procedure but a careful explanation and understanding of the effectiveness of using local anaesthetic ointments may well allow the blood sampling to be performed with little distress. The same could be applied for infants who will have no understanding prior to the procedures being performed. Such provisions to minimise even the smallest of risk within the research design is important.

4.4 Parental Judgement

While parents are judged constantly by fellow parents and the wider community in their decision-making towards their child's welfare, as a society we allow parents the right and responsibility to make such decisions concerning the welfare of their infant or child without intervening. Decisions that parents make often take into account the best interests of the family as a unit, rather than of each individual child. For instance, moving to another city and moving schools because of better job prospects are advantageous for the family as a unit but may not be the best interest of one child at any given time given a child may be uprooted from his or her school and friends. These intra-familial trade-offs occur on a daily basis within the family unit with trivial situations such as decisions on where the family should go for dinner with every

[161] Ibid.
[162] Ibid.

member of the family having their favourite place to eat. Translating this concept into decision-making for infants in research, we must continue to allow parents the right and responsibility to make practical and informed decisions regarding allowing their infants to participate in research, whether it is therapeutic or non-therapeutic research. Parents should be given the responsibility to ensure that their infant's best interests are not undermined and be allowed to make an informed decision which also takes society's interests into account with regards to the need for research and its benefit for the greater good.

Achieving an acceptable balance between the social good in research, ensuring that parents are fully informed of minimal risk and the obligation to protect infants who participate in research remains a challenge that should lie with giving parents the rights and responsibilities to make such decision. Singer remarks that adults can be motivated by an altruistic desire to do good for society, and as such will choose to participate in research even if the research has no direct personal benefit and may even impose some risk or discomfort.[163] The philosopher David Wendler remarked on the life of Irmgard Hunt, born in Germany in 1934, who encountered Hitler and his entourage in a park when she was 3 years old and was subsequently photographed sitting on Hitler's lap. In a memoir published by Hunt many years later, she expressed concern that the photo of her and Hitler was used for Nazi propaganda. Wendler interprets Hunts' comments that she would have felt guilty that she may have passively contributed to the Nazi cause.[164] This interesting analogy shows us that one's life can be affected in a negative manner if somehow one had contributed to an event that was bad even if it was at an age where one was too young to take any responsibility for those early actions. If we transposed this concept to research participation, then we can infer that the infants who grow up to be adults would be equally justified in thinking that it is good for them that they were able at a young age to contribute to the development of a better treatment for a childhood disease from their participation in research, even if they were too young to make the decision at the time.

[163] Singer P. (2011) 'When is research in children ethical?', *The Lancet*, 377 (9760): 115.
[164] Wendler D. *The Ethics of Paediatric Research*, (Oxford, Oxford University Press, 2010).

If adults can see that their participation in a research project as something that makes their life more meaningful, and hence is within their interests,[165] can they also ethically make the same choice for their child? This is possible and we can justify making these decision as parents who are responsible for their infants' welfare to allow infants who lack capacity to participate in research studies without abandoning the principle that it is wrong to use infants in research that will not benefit them. To decide when research with infants is justifiable, we must therefore take a stance somewhere on the middle spectrum between protection of the infant's rights and achieving the best consequences for the greater good, and ultimately parental choice and information given to parents is an important factor.

[165] Truong TH, Weeks JC, Cook EF, and Joffe S. (2011) 'Altruism among participants in cancer clinical trials', *Clin Trials*, 8(5): 616-623.

CHAPTER 5: INFORMED CONSENT

This chapter discusses how consent in children is taken and interpreted in the context of research. It will critically explore the different nuanced approaches to how the process of consent has been developed to accommodate different types of situations such as deferred consent and presumed consent.

5.1 What is Consent?

"Consent" describes the positive agreement of a person, whilst "assent" refers to acquiescence.[166] Both words may mean agreement but assent may just mean a preference. The common law of consent is determined by the courts. The legal recognition for the principle for consent is that "every human being of adult years and sound mind has the right to determine what shall be done with his own body" predates modern constitutional jurisprudence.[167] In 1765 Blackstone described a common law right to bodily integrity as including a right to "the preservation of a man's health from such practices as may prejudice or annoy it".[168] Courts have always upheld a person's right to decide how his or her own body should be protected and the courts have consistently rejected any claims that the medical profession or the state have a right to force, impose, dictate or withhold an individual's medical treatment. In *Re T* (Adult: Refusal of medical treatment),[169] a young woman who was 34 weeks pregnant and a Jehovah's Witness, refused a blood transfusion after a road traffic accident but the Court of Appeal allowed the blood transfusion to proceed in the emergency situation. Lord Staughton in the judgement stated that "an adult whose mental capacity is unimpaired has the right to decide for herself whether she will or will not receive medical or surgical treatment, even in circumstances where she is likely or even certain to die in the absence of treatment". Lord Donaldson also said that "this situation gives rise to a conflict between two interests, that of the patient and that of the society in which he lives. The patient's interests consist of his right to self-determination - his right to live

[166] McIntosh N. (2001) 'Guidelines for the ethical conduct of medical research involving children: Royal College of Paediatrics and Child Health - Ethics Advisory Committee', *Arch Dis Child*, 82: 177-182.
[167] Blackstone W. *Commentaries on the Laws of England* (London, London Publishing Co., 2007), 134.
[168] Ibid.
[169] *Re T* (Adult: Refusal of medical treatment) [1992] 4 All ER 649.

his own life how he wishes, even if it will damage his health or lead to his premature death".[170] The case illustrates how important it was to have individual consent to a medical intervention in any circumstances.

5.2 Consent for Children and Infants

In the UK, consent with respect to children is taken to mean consent from parents or the guardian.[171] Discussion surrounding children's competence and ability to consent to any medical treatment has focused on the age of the child and the capacity for the child to understand what is being proposed in terms of his/her participation, and it is the child and not their parents/guardian whose consent is required by law (this was termed as "Gillick-competence" which arose from the seminal House of Lords decision in 1986).[172] If there is dissent from a child or a reasoned refusal to participate in research, this is often regarded as evidence of such understanding by the child, and parental consent in these circumstances would be disregarded.[173] The researcher in those circumstances must respect the will of the child if they decline to participate in the research study. The law does not at this current time have any form of a benchmark for a minimum chronological age but it perceives that a degree of maturity and understanding from the child should be taken into account. However, it is important to note that in the case of infants, there is insufficient maturity or competence to consent in any participation of treatment or research, and therefore 'parental consent' must be obtained.

In principle 11 of the Declaration of Helsinki,[174] in the case of minors it does stipulate that "permission of a responsible relative replaces that of the subject in accordance with national legislation". In SI 2004/1031 of the EU Clinical Trial regulations in 2004, it states that "a person with parental responsibility can give informed consent on behalf of a minor, with mothers always having the parental

[170] *Re T* (Adult: Refusal of medical treatment) [1992] 4 All ER 649 at 661.
[171] General Medical Council (2013) Parents and parental responsibility. Accessed 3rd December 2013 http://www.gmc-uk.org/guidance/ethical_guidance/children_guidance_appendix_2.asp
[172] *Gillick V West Norfolk and Wisbech AHA* 1986 A.C 112. The case discussed the issue of a minor being able to consent rather than the notion of 'parental rights' or parental powers. The court held that 'parental rights' did not exist other than to safeguard the best interests of a minor and that in some circumstances a minor could consent to treatment, and that in these circumstances a parent had no power to veto treatment.
[173] See n159.
[174] World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (revised 2008) Accessed 2013 at www.wma.net/en/30publications/10policies/b3/.

responsibility".[175] Unwed fathers do not automatically have parental responsibility for consenting on behalf of their child but they can acquire parental responsibility by being named on the child's birth certificate, applying for and getting a residence order or a parental responsibility order, making a parental responsibility agreement with the biological mother in a set procedure or being appointed as guardian of the child once the appointment takes place, or marrying the mother.[176] A step-parent may also gain parental responsibility by obtaining a residence order or adopting the child.[177] Therefore, in the context of research involving infants, whoever holds parental responsibility is therefore responsible for the infant's best interests and ultimately signs the consent for the research to proceed, taking into account the information given on risks and benefit.

Examples of research experimentation with children date back centuries. However, parental consent for children were often taken for granted. Lederer and Grodin observed that medical physicians often used their own children to conduct immunisation "experiments" or as research subjects on infectious diseases because the children were convenient and easily accessible.[178] One widely cited example from the 1790s is Edward Jenner's experimental injection of his gardener's son and his own son with the cowpox virus to vaccinate them against smallpox.[179]

The physical integrity of children is protected by the law today and the regulatory framework discussed so far stipulates that it may be against the interests of a child to compromise in any way 'more than minimal' the child's physical or psychological comfort. Any forms of research conducted in children or infants must have the consent of the parent, guardian or child.[180] There is a general exception that is

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[175] UK Medicines for Human Use (Clinical Trials) Regulations at Www.Uk-Legislation.Hmso.Gov.Uk/Si/SI.2004/1031, accessed 3rd January 2013.

[176] Section 2(2) of the Children Act 1989 provides that where the mother and father are unmarried at the time of birth, only the mother will have automatic parental responsibility for the child. The unmarried father does not have parental responsibility unless he acquires it by: i) Registering the birth of the child together with the mother - s 4 (1)(a) ii) Formal agreement with the mother – s 4(1)(b), iii) Court order, following an application by the father – s 4(1)(c) or iv) Residence order – s 12(1) see Appendix C for further information on the 'Status of Unmarried Fathers'.

[177] Children's Act 1989, Section 8 states "A Residence Order" means an order settling the arrangements to be made as to the person with whom a child is to live.

[178] Lederer M and Grodin M (Eds.). *Children as Research Subjects: Science, Ethics and Law* (New York, Oxford University Press, 2010), 3-5.

[179] Ibid.

[180] Eekelaar J. (1994) 'The interests of the child and the child's wishes: the role of dynamic self-determinism', *International Journal of Law and the Family*, 42: 46.

debatable to obtaining prior parental consent in situations whereby there is immediate provision of medical care in an emergency situation where research of a treatment is being carried out. In this situation, it may be impracticable to even attempt to obtain prior informed consent for the proposed research procedures from parents or guardians during that time.

5.3 Deferred Consent

In an emergency situation when parental consent cannot be obtained prior to the treatment, and when we do not know which is the better treatment option in critical situations, then seeking consent in emergency care is unethical if it delays trial treatment and obscures or reduces treatment effects.[181] There have been two studies described which were undertaken in paediatric emergency departments whereby the principle of necessity was used. Both these studies were randomised controlled trials of anticonvulsants in acute convulsive seizures and the process of consent used was 'deferred consent'.[182] The studies both received full ethical approval and support, were accepted by over 98% of the participating families and their results have led to a change in practice throughout the UK.[183] In another study, deferred consent was reported to be acceptable to most parents and carers of children who had received emergency care and had their consent 'deferred' in randomised trials of emergency treatments.[184] Interestingly, there have been many trials that have successfully used this approach of deferred consent based solely on the urgent need to treat.[185]

[181] Roberts I, Prieto-Merino D, Shakur H, Chalmers I, and Nicholl J. (2011) 'Effect of consent rituals on mortality in emergency care research', *Lancet*, 377: 1071.
[182] Appleton RE, Sweeney A, Choonara I, et al. (1995) 'Lorazepam vs. diazepam in the acute treatment of epileptic seizures and status epilepticus', *Dev Med Child Neurol*, 37: 682-6; and McIntyre J, Robertson S, Norris E, Appleton R, Whitehouse W, and Phillips B. (2005) 'Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomized controlled trial' *Lancet*, 366: 205-10.
[183] Gamble C, Woolfall K, Young B, Williamson P and Appleton R. (2012) 'Deficiencies in proposed new EU regulation of clinical trials', *BMJ*, 345.
[184] Gamble C, Nadel S, Snape D, McKay A, Hickey H, and Williamson P. (2012) 'What parents of children who have received emergency care think about deferring consent in randomised trials of emergency treatments: postal survey', *PLoS One*, 5.
[185] Maitland K, Molyneux S, Boga M, Kiguli S, and Lang T. (2011) 'Use of deferred consent for severely ill children in a multi-centre phase III trial', *Trials* 12: 90; and National Institute for Health Research Health Technology Assessment Programme (2011) *CATheter Infections in Children: The CATCH Trial.*

However, to require such an attempt to obtain parental consent may also inhibit much potentially valuable research. In this situation, it is prudent to obtain prior ethical approval from relevant research ethics committees so that it may be ethical to conduct any form of research on children in situations of extreme urgency without obtaining prior consent. It may still be unlawful if the research were not expected to benefit the child and in all cases parents or guardians and, where appropriate, the child must be informed about the research as soon as possible afterwards: a requirement in ethics as in courtesy. The current European Clinical Trials Directive[186] had set specific regulations on valid informed consent as the cornerstone of conducting any experimental research involving human beings. However, Gamble argued that the EU regulations and Directive had made no provisions for consent during emergency situations, therefore creating a formidable barrier to research in this setting. As a result, Member States have been forced either to operate at variance with the Directive or to accept restrictions in emergency care research, and the EU Directive has been acknowledged to have hindered the conduct of clinical trials across Europe.[187]

The GCP regulations stipulate that for children below the age of assent - such as neonates, infants, toddlers, and young children - parents are the sole decision-makers as to whether the child will participate in research.[188] In clinical research pertaining to therapeutic or non-therapeutic trials, a parent or legal representative of the child may give consent to the full participation of the trial whereby full information has been given including aims of the trial, objectives, risks, inconveniences, conditions and the right to withdraw from the trial at any point in time.[189] There must also be no financial gains from participating in any research other than compensation for loss of time from work, transport or any subsequent injury. In addition, any pain, fear, discomfort or any predicted risk must be disclosed and minimised by the conduct and design of the research study with the age of the research participant and relevant disease in mind such that the trial must relate to a condition that the child may have, and such risks be

[186] EU Clinical Trials Directive (2006) at Www.Wctn.Org.Uk/Downloads/Eu_Directive/Directive.Pdf.
[187] Gamble C, Woolfall K, Young B, Williamson P and Appleton R. (2012) 'Deficiencies in proposed new EU regulation of clinical trials', *BMJ*, 345.
[188] Ibid.
[189]Good Clinical Practice 2013 accessed April 15th 2013 at: www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/index.htm.

specifically defined and monitored throughout the trial.[190] In the case of infants, the entire power of consent lies with the parent or guardian. The omnipotence of parents leaves a child completely vulnerable. Lansdown[191] stated that infants were inherently vulnerable because of their physical weakness, their lack of knowledge, capacity or competence, and their lack of experience which renders them completely dependent on the adults around them. Children's vulnerability means that there is a fundamental difference in the way researchers work with a vulnerable child compared to an adult subject in terms of obligations and responsibilities. Researchers also need to recognise that their moral duty and obligations are as adults to protect the child from harm or risk even when this may mean losing access to the child with respect to research recruitment.

Prompt decision-making may be critical in emergencies and in cases such as neonatal resuscitations, use of surfactant treatment in preterm deliveries, different modes of ventilatory support and treatment of seizures, there is very little time for parents to consider participation into a clinical trial as fast decision-making is required. Studies have shown that any reasonable understanding is severely compromised in situations that are stressful and that parents are substantially influenced in their decision to consent and participate in trials under these circumstances.[192] Furthermore, such stressful and parental anxieties are often associated with making decisions on behalf of one's child, especially one's sick child, which can in turn put particular stress and affect an adult's reasoning, comprehension, and decision-making capacities.[193] Zupancic and colleagues[194] found that a small minority of parents would have preferred that their doctor advised them on whether to allow their infant child to participate in a research study rather than having to decide for themselves. This can be considered unlawful if the research was not expected to directly benefit the child and would undoubtedly override the autonomy of the parents. However, where there are exceptional cases of medical emergencies, under the doctrine of necessity, medical treatment is permitted without

[190] See n153.
[191] Lansdown, G. 'Children's rights' in B. Mayall (ed.) *Children's Childhood: Observed and Experienced* (London, The Falmer Press, 1994).
[192] Hewlett S. (1996) 'Consent to clinical research: adequately voluntary or substantially influenced?', *Journal of Medical Ethics*, 22(1): 232-37; and Manning DJ (2000) 'Presumed consent in emergency neonatal research', *Journal of Medical Ethics*, 26(1): 249-53.
[193] Ibid.
[194] Zupancic JA, Gillie P, and Streiner D. (1997) 'Determinants of parental authorisation for involvement of newborns in clinical trials', *Pediatrics*, 99(2): 117.

consent from the parent or a competent child.[195] It is important to note that with deferred consent - although practically constructed and accepted by research communities - there is no legal construction to its process and the European Clinical Trials Directive had made no provision nor reference to allow consent to be presumed even in emergency situations.

5.4 Presumed Consent

Another area that is debatable is 'presumed consent' and where antenatal consent is sought from the parents. However, such an approach has been criticised because parents may pay little attention to the research information given before their child is even born in a belief that their infant will be unlikely to be affected by the particular condition. This form of consent has been described for example in neonatal resuscitation trials in which a newborn infant develops respiratory distress and the intervention must be instituted immediately.[196] The process of obtaining consent in the conventional way for such situations is not practicable or feasible. Interestingly, the 'opt out' consent processes had been used and was argued that it protects vulnerable families and deprived families who may not have the level or understanding of the rationale of the research or the consent process to be able to give consent and participate in the study. Rogers and colleagues[197] found that the option of the 'opt out' consent process better facilitated research studies and allowed parents to participate in trials which produced more generalisable conclusions to research questions and reduced study selection bias. In addition, up to 83% of parents who consented would not have retracted their prior consent when asked again and only 8% of parents were unhappy with giving their consent at the time. The legality of such an approach must be questioned as the pre-requisite of any research study must be that the best interests of the child must be taken into account during the full consent process.[198] Moreover, in light of current ethical and legal legislations within GCP and EU Clinical Trials Directives, there is no place for the

[195] The principle of necessity is described in *F v West Berkshire Health Authority and Another* [1989] ALL ER 545.
[196] Yagui AC, et al., (2011) 'Bubble Cpap versus Cpap with variable flow in newborns with respiratory distress: a randomized controlled trial', *J Pediatr (Rio J)*, 87(6): 499-504.
[197] Rogers CG, Tyson JE, and Kennedy KA. (1998) 'Conventional consent with opting in versus simplified consent with opting out: an exploratory trial for studies that do not increase patient risk', *Journal of Pediatrics*, 132(1): 606-11.
[198] Ibid.

terms ‘opt out’ or ‘presumed consent’ processes today and it must be deemed unlawful and unethical as it implies that a parent of an infant would always consent to the research without questioning the integrity of the research or the potential harm or risk the participation may cause.

5.5 Process of Consent

The principle of respect for the person underpins the emphasis on the confidentiality of personal information and the provision of consent for both medical treatment and research participation in therapeutic and non-therapeutic research.[199] Voluntary participation in research allows the research participant to have the freedom to withdraw at any time from a research study.[200] The informed consent process is essential in any form of research undertaken and researchers must have an adequate understanding of the process of how the research is being conducted, how the consent procedure is explained and to ensure adequate understanding of the research by the participant. In the UK, researchers who undertake the informed consent procedure must complete also the Good Clinical Practice course.[201] Article 3 of 2005/28/EC stipulates that the informed consent process must be undertaken in accordance with the Declaration of Helsinki:

> In any research on human beings, each potential subject must be adequately be informed of the aims, objectives, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to the participation of the research at any point in time.[202]

This translates to the fact that each participant must have adequate information, knowledge and understanding of the research study in question, despite it being either diagnostic, therapeutic or a preventative intervention. It also means that they must have

[199] Field MJ and Behrman RE. *Ethical Conduct of Clinical Research Involving Children* (Washington, Natinal Academies Press, 2004).
[200] Ibid.
[201] See n181.
[202] Ibid.

an understanding of why the research is being done, what is the potential harm or risk attributed, what are the potential benefits of being in the research and what other interventions are currently available. The purpose of this consenting process is also to allow the participant the absolute right to leave the research at any time without having to give a reason and without giving up their legal rights. The process of informed consent allows and ensures that the individual has control over what they are embarking on by being in the research study and it ensures that they are participating in the research when it is consistent with their values, judgments and interests.

The RCPCH published research guidance which stated that legally valid consent process is both freely given and informed. For consent to be freely given researchers must offer families no financial inducement, although expenses should be paid such as for travel or loss of work, exert no pressure on participants or their families, allow as much time as possible to consider whether they wish to participate in the research, be allowed to withdraw or refuse to participate at any time even if a consent form has been signed without having to give a reason for the withdrawal and be assured that non-participation in the research will not prejudice the patient's current treatment.[203]

When explaining relevant terms, researchers need to discuss with families the consent implications of the study. For example, consenting to a double blind randomised trial means not minding which choice of treatment - for instance, intervention versus placebo or novel versus conventional options that the child will receive - and that neither the family nor their doctor will know which treatment has been given until the trial has been completed. These guidelines were designed to benefit children who take part in research, children who may be helped by the research findings, and medical research itself. Researchers who observe high standards will continue to have public support and cooperation. The guiding principles for research were implemented to guide and aid those who make decisions for infants who are incapable of making those decisions themselves. It is important therefore that those who make those decisions have the infants' best interests at heart.

[203] See n153.

Parental consent will probably not be valid if it is given against the infant's welfare and interests.[204] This means that parents can consent to research procedures that are intended directly to benefit the child, but that research that does not have any direct benefit to the research subjects (such as non-therapeutic research) can only be validly consented to if the risks are minimal or negligible and that the research can be reasonably said not to go against the child's interests.[205] The RCPCH takes the view that provided the research cannot be carried out in adults, and appropriate risk/benefit assessment is carried out, non-therapeutic research is ethical.[206] Account must be taken of whether non-therapeutic research is necessary and needed in infants because they do not respond to drugs the way adults or older children do. Although there is an ethical argument to support non-therapeutic research from medical bodies such as the RCPCH, it is only lawful if accepted by the courts. In the absence of any clear legal guidance in this area, any authorisation of non-therapeutic research involving infants who are incompetent would not be deemed to be in the infant's best interest when he/she does not stand to gain from the research participation. Parental consent in this area cannot be deemed as sufficient to render this lawful nor would it be ethically justifiable. The law remains unclear on any proposed non-therapeutic research involving infants, particularly where there is concern that the risk involved is more than minimal. The difficulties in how we determine best interests compared with utilitarian views will be fully considered in Chapter 6.

5.6 Flaws in Parental Consent

Some would argue that in the case of infants, the informed consent process itself is flawed and can give rise to feelings of powerlessness amongst parents. The consent process for infants may be deemed as unethical if parents are emotionally unready, are not fully informed or may not have the right level of understanding with regard to the research information given. Mason and Allmark reported[207] that the informed consent process itself may give rise to misunderstanding on the part of parents of infants

[204] Elliston, SD. *The Best Interest of the Child in Healthcare* (London, Routledge, 2007), 40.
[205]Edwards, S. and Mc Namee MJ. (2005) 'The ethical concerns regarding guidelines for the conduct of research on children', *Journal of Medical Ethics*, 34: 252-259.
[206] See n153.
[207] Mason SA and Allmark PJ. (2000) Obtaining informed consent to neonatal randomised controlled trials: interviews with parents and clinicians in the Euricon study', *Lancet*, 356: 2045-51.

recruited to a neonatal trial and this was more evident amongst those who were poorly educated and emotionally stressed. In another case, relating to a continuous negative extrathoracic pressure (CNEP) trial, doctors were said to have "sold" the idea of research participation to parents by stating if the study was a kinder, gentler treatment and that they had been reported to have avoided the consent issue because they wanted to protect the infants, without at any point informing parents that it was a clinical trial.[208] In previous reported studies, from 3.5% to 12% of parents did not even remember that they had given consent and parents felt that the discussion surrounding the consent process was inadequate and did not provide enough information with regard to alternative options from the novel research or the scope of the research protocols and methodologies.[209] Another study also found that 25% of parents who were approached to participate in research for their child, felt obligated to participate due to a feeling of being dependent on the investigator or the hospital.[210] A recent study suggested that many of the parents, at the time of recruitment to research studies, were concerned about their child's condition and treatment and viewed the research as an opportunity to obtain otherwise unavailable medications.[211] Parents were also inclined to view participation in research as a means of guaranteed benefits.[212] Parents may also feel guilty when dealing with a sick infant or feel coerced into the process of being asked to participate in research at a vulnerable or critical time when their child is unwell.[213] These findings point to a high state of parental stress and anxiety, and the frequent sense of not having any real choice. In neonatal research, the mother may be too exhausted or tired to mentally absorb all the information given. In some cases, cognitive function may also be impaired if the mother is sedated or had analgesia.[214] It can be argued that all these forms of research trials have flawed consent processes which may be deemed as unlawful based on current GCP regulations.

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[208] Smith RL. (2000) 'Babies and consent: yet another NHS scandal', *British Journal of Medicine*, 320: 1286-86.
[209] Stenson BJ and Becher JC. (2004) 'Neonatal research: the parental perspectives', *Archives of Disease in Childhood*, 8(F321): 5; and Mason and Allmark, above n199.
[210] van Stuijvenberg M, Suur MH and de Vos S. (1998) 'Informed consent, parental awareness and reasons for participating in a randomised controlled study', *Archives of Disease in Childhood*, 2: 120-25.
[211] Shilling V, Williamson PR, Hickey H, Sowen E, Smyth RL and Young B.(2011)'Processes in recruitment to randomised controlled trials of medicines for children (RECRUIT): a qualitative study', *Health Technol Assess*, 15(15): 1-116.
[212] Ibid.
[213] Ibid.
[214] Snowdon C, Elbourne D, and Garcia J. (2006) 'It was a snap decision: parental and professional perspectives on the speed of decisions about participation in perinatal randomised controlled trials', *Soc Sci Med*, 62(9): 2279-90.

5.7 Deficiencies in Consent Forms

A systematic analysis review of 124 consent forms provided for HIV and AIDS research in the US and abroad about study protocol, procedures, risks and benefits found that consent forms were too long, spanning 20 pages on average and exceeding recommendations for how much information readily can be processed. [215] The language and wordings on the consent forms used were also deemed too complex and enough to hinder participants' full understanding of the research.[216] Nancy Kass, the author of the study, concluded that by making the informed consent forms long and complex, the researcher neglected their ethical duty to ensure the research was described in a way that the participant could truly understand. Commonly misunderstood concepts in research (such as randomisation or placebo) were not explained and given little attention whilst confidentiality sections had a median length of two pages compared to fifty-three words in explanations of the randomisation procedures.[217] In 2013, the Office for Human Research Protections in the US issued a statement[218] claiming that the Federal Government had taken a fundamental step toward addressing a highly unethical trial involving premature babies. The trial - the SUPPORT study[219] - was funded by the National Institutes of Health and the trial involved 23 academic sites in the country which took part in conducting a clinical therapeutic trial in premature babies born between 24 and 27 weeks gestation who were already at risk of death or eye disease. The study tested two methods for regulating oxygen treatment in premature babies which were experimental: one group were maintained at a low blood oxygen level and the other at a high level of oxygen saturation. The trial led to 1,316 premature infants being exposed to an increased risk of blindness as a result of higher oxygen saturation levels without informing the parents of the risks to their infants. Further analysis of the

[215] Kass NE, Chaisson C, Taylor HA, Lohse J. (2011) 'Length and Complexity of US and International HIV Consent Forms from Federal HIV Network Trials', *Journal of General Internal Medicine*, 6(11): 1324-1328.
[216] Ibid.
[217] Ibid
[218] *The Office for Human Research Protections Reaffirms Main Findings of Inadequate Informed Consent for Premature Baby Study, But Bows to Political Pressure and Puts Enforcement Actions Hold* at www.citizen.org/pressroom/pressroomredirect.cfm?ID=3905 acccessed 23rd June 2013.
[219] The SUPPORT Principal Investigators (1995) 'A controlled trial to improve care for seriously ill hospitalized patients: the study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT)', *JAMA*, 22-29: 1591-8.

trial protocol and consent forms from the 23 institutions demonstrated that deficiencies in the consent forms given to parents had failed to disclose the true purpose of the research, the risks and the nature of important experimental interventions.

The general aim of any prospective research is to enable the research participants to have a basic understanding of the nature of the research, the processes, purposes and risks involved within it. Research trials which involve random assignment to treatment and control groups must be clearly explained, and any consent forms and permission forms must be written in a way that is easily understood with any potential for risks or harms described. Researchers often compensate for any shortcomings in consent forms during the consent process by discussing with parents and exploring parents' understanding of the research study in relation to their infant. However, little is known about such conversations during recruitment and any failure to fully explain the research study constitutes an important deficit within the informed consent process.[220]

5.8 Deferred Consent in Emergency Situations

The 2001 European Clinical Trials Directive[221], incorporating the ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH GCP)[222] regulations, produced fixed guidance on what constitutes 'informed consent' in clinical research. The Directive, however, made no reference or provisions for consent in emergency situations. European Member States were forced either to operate at variance with the Directive or to accept significant restriction of these types of research.[223] Internationally, guidelines on emergency consent vary or are not specifically addressed. Legislation to incorporate a deferred consent process in emergency situations for incapacitated adults and for children were incorporated in 2006 and 2008 in the UK if: (1) urgent treatment was necessary; (2) urgent action was needed for the purposes of the trial; (3) it was not

[220] Edwards, S. and Mc Namee MJ. (2005) 'The ethical concerns regarding guidelines for the conduct of research on children', *Journal of Medical Ethics*, 34: 252-259.
[221] European Clinical Trials Directive (2001) *Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use*.
[222] Medicines for Human Use (Clinical Trials) Regulations, 10 S.I. 2004/1031 at www.opsi.gov.uk/si/si2004/20041031 accessed 14th April 2013.
[223] Maitland K. (2011) 'Use of deferred consent for severely ill children in a multi-centre Phase 3 trial', *Trials*, 12.

reasonably practicable to obtain consent prospectively; and (4) approval to the procedure was obtained by an ethics committee.[224] This process of deferred consent allows research patients to be included in research trials without obtaining their prior informed consent or that of their parent or carer (in the case of a legal minor), but requires that informed consent is obtained as soon as possible for continued study participation.[225] However, strict guidance includes wordings which are ambiguous, and studies have shown that it has consequently deterred trauma investigators from pursuing valuable research endeavours. In particular, the language requiring "community consultation" and evidence-based demonstration that existing treatments are "unproven or unsatisfactory" must be identified as the most problematic terms to satisfactorily address by those aiming to conduct trauma research. Surprisingly, although current regulations as described were enacted to guide consent requirements in emergency research in order to protect such vulnerable populations (such as infants) from exploitation, these same regulations may also serve as barriers to clinical trials in trauma research, resulting in depriving this population of infants of benefits of advances from research in trauma.[226]

In the case of the TIPIT research study on preterm infants,[227] some parents had expressed concern and distress as to whether their preterm infant were to be randomised to a conventional treatment, taking the assumption that the treatment arm was the better alternative for their infant who was gravely ill at the time. Their worry was further compounded by the uncertainty of whether the research was to be beneficial or may cause harm in the first place despite efforts to explain the aims and scope of the research. The sense of obligation and anxiety parents experienced during this consent process would certainly indicate that the entire consent procedure was inadequate and 'non informed'. It has been shown in a study that parents may not understand that the treatment has been selected at random and that some parents thought that in a

[224] The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations SI.2006/2984 at www.opsi.gov.uk/SI 2006/2984 accessed 4th April 2013.
[225] Gamble C. (2012) 'What parents of children who have received emergency care think about deferring consent in randomised trials of emergency treatments: postal survey', *PLoS One*, 7(5) 45.
[226] Morrison CA, Horwitz IB, and Carrick MM. (2009) 'Ethical and legal issues in emergency research: barriers to conducting prospective randomized trials in an emergency setting', *J Surg Res*, 157(1): 115-122.
[227] Ng SM, et al., (2009) TIPIT: a randomised controlled trial of thyroxine in preterm infants under 28 weeks' gestation', *Trials*, 9(17): 21.

randomised trial, their doctor would ensure that their child would receive the best treatment offered and some believed that randomisation meant rationing access to difficult clinical decisions.[228] Parents who are approached to consent for their child's participation in clinical trials when their child is ill are often making decisions under extreme stress. Snowdon also found that many parents choose to trust the physician's assessment rather than make their own decision especially if the recruiter is in the medical team.[229] In contrast, 88% of parents in a double-blind randomised controlled trial were fully aware that their child may be given a placebo treatment instead of ibuprofen, an active antipyretic in a study of the prevention of recurrent febrile seizures.[230] Such diverse observations show that differences may be attributed to the educational background and state of mind of parents, the nature of the research study or the complexity of the research protocols.

5.9 Inequality between Researcher and Parent

There is also a difference in power between parent and the 'doctor-researcher' whereby the parent may fear that their infant would be treated differently if he/she does not consent to the request by the doctor for participation in the research within the unit. It is evident that the relationship between the researcher and the parent is unequal in power and the researcher is seen as someone imbued with knowledge. Factors that may exacerbate the situation during the consent process may be an ill child as a potential research participant or being in unfamiliar surroundings. Is there a conflict of interest from researchers with the current need for achieving adequate recruiting targets? Can the researcher remain impartial at the point of information giving and consent? We must recognise the vulnerability of the research subject who is the infant as well as the parent. The relationship between the researcher and the participants are unequal and factors such as an ill infant, unfamiliar surroundings, and highly stressful circumstances further exacerbates the already unequal power relationship within the research environment. Overall, studies point to the need for particular care in the design and review of

[228] See n206.
[229] Ibid.
[230] van Stuijvenberg, Suur, and de Vos. (1998) 'Informed consent, parental awareness and reasons for participating in a randomised controlled study', *Archives of Disease in Childhood*, 79: 120-125.

processes for seeking parental permission for research that will involve seriously ill children and high-stress situations.

There is also a potential conflict of interest from the parent/guardian if certain research studies should provide significant reimbursement for the study participation of their child as a token gesture. One would question if this was unethical as the pre-requisite of any ethical research study participation would be that no one should have any direct benefit from the participation. If there is risk of harm or potential side effects to the intervention, then parents who consent are not acting in the best interests of the child but may gain direct personal benefit if any form of remuneration was provided for their child's participation. Remuneration for personal gain or as enticement to participate in research trials is not allowed,[231] yet many research trials will remunerate parents by payments or vouchers given to reimburse travel expenses, to compensate for time off from work, inconvenience and possible discomfort and to show a token appreciation for participants' help, or to pay for people's help.[232] The issue of compensation or paying research participants raises ethical questions as there is no clear guidance or consensus on this topic but any form of compensation must never override the principles of freely given and fully informed consent. Consent by proxy for infants will be a significant concern if such incentives are used and one would question who benefits more from the participation. Children are therefore susceptible to greater abuse because their interests are not adequately protected. We want infants to be able to benefit from the advances and accelerating rate of progress in medical care that is fuelled by scientific research. However, we do not want to place any infant at any risk of harm from participating in any research even if their very involvement may be essential to improving the overall medical care of future populations. Although arguments for the future health of infants and children are dependent on the performance and access of clinical research in which infants participate, it is important that infants are protected in research. The current research literature relates to regulations in infants is limited and not entirely consistent although it supports a gradual expansion of the involvement of

[231] Note the Standards of the 1947 Nuremberg Code state that no persuasion or pressure of any kind should be put on participants.

[232] Head, E. (2009) 'The ethics and implications of paying participants in qualitative research', *International Journal of Social Research Methodology*, 12: 1464-5300; and Wendler D, Rachoff J, Emanuel E, and Grady G. (2002) 'Commentary: the ethics of paying for children's participation in research', *Journal of Paediatrics*, 141(2): 166-171.

children and infants in discussions and decisions about their participation in research. All of those responsible for research involving infants and children need to understand the special ethical issues and regulations that are relevant to the conduct of such research and the additional protection that must be provided. In certain cases, ethical standards must prevail and may preclude some otherwise desirable research.

Although some would argue and object to the idea of parents consenting to their infant's participation in any research that causes them distress, pain, risk of long-term harm, why should parents who are fully informed not be able to consent when the research carries no more than a minimal risk of significant harm? Parents have such rights and responsibilities to be able to consent to the involvement of their child in a well-designed research study that would benefit future populations of similar age even though the process involves drawing blood, and that doing so would involve only momentary pain and a minimal risk of infection which can be considered negligible.

CHAPTER 6: BEST INTERESTS VERSUS UTILITARIAN JUDGEMENT

6.1 Utilitarianism and Research

Utilitarianism is defined as the idea that we as individuals will choose the morally correct course of action, the one that produces the greatest total benefit for all people affected.[233] Research has shown that people's individual differences relating to emotion and personality influence their utilitarian judgments and diverse emotions were elicited during judgment such as guilt, sadness, disgust, empathy, anger and anxiety.[234] In the trolley dilemma analogy by Greene, Sommerville, Nystrom, Darley and Cohen,[235] a runaway trolley is headed for five people who will be killed unless steps are taken to stop it. The only way to save the five people was to hit a switch that will turn the trolley onto another alternate track where it will kill one person instead of five people. Should you hit the switch and turn the trolley in order to save five people at the expense of one person? In this scenario, most people in the survey said yes they would hit the switch. In contrast to another scenario, Greene and colleagues describe the footbridge dilemma whereby you are standing next to a stranger on a footbridge that spans over the track, in between the oncoming trolley and the five people. In this situation, the only way to save the five people was to physically push the stranger off the footbridge onto the tracks below. If you push the stranger, he will inevitably die but his body will stop the trolley from reaching and killing the other 5 people. Should you save the five others by pushing this stranger to his death? Most people said no in this survey.[236] The differences, according to Green and colleagues, from the two scenarios and differing answers obtained between the trolley dilemma and the footbridge dilemma were due to one example being an impersonal moral dilemma and another a personal moral dilemma.[237] It is the same dilemma with a difference between actively killing someone or subjecting someone to be killed. The different emotions described do not make it the right moral

[233] Sinclair J, Knight LS and Clari M (eds.) *English Dictionary for Advanced Learners* (Glasgow, Harper Collins, 2001).
[234] Choe SY and Kyung-Hwan, M. (2011) 'Who makes utilitarian judgments? The influences of emotions on utilitarian judgments', *Judgment and Decision Making*, 6(7): 580-592.
[235] Greene JD, et al. (2001) 'An fMRI investigation of emotional engagement in moral judgment', *Science*, 293: 2105-2108.
[236] Ibid.
[237] Ibid.

choice. Green further argued that using personal ethical and moral scenarios allowed emotional engagements to influence only personal moral situations. The ethical parameter within which ethical decisions or choices take place is ambiguous. We assume that the role of medical ethics or the law will guide us to the right choice but, arguably, the 'right choice' may not be everyone's 'right choice' and the law can often 'bend' towards an option that may be more perverse and the boundaries where our acceptance lies are often moved. While the utilitarian approach to morality implies that no moral act is intrinsically right or wrong, the deontological ethics is about the nature of the action which is either right or wrong and consequences of the action do not matter.

Interestingly, the principle argument justifying medical research in infants is utilitarianism. Foster states that "Utilitarianisn has the advantage of simplicity such that it only considers the outcome of actions to matter morally and inherent to this approach is the disadvantage that it can justify or require harm to some." [238] Utilitarianism therefore fails to offer sufficient moral basis for considering whether the particular research conducted in infants is morally acceptable or not as long as it is for the greater good.[239] Cantor suggested that unless mentally incompetent persons are used in medical no therapeutic research, then similar future generations of non-competent persons will be deprived of medical advances.[240] This can be transposed to similar research in vulnerable infants who do not have capacity to make decisions for themselves. The importance of research that can only be done in this population is argued to be justified by the fact that the social gains outweigh the minor impositions on the mentally incompetent subject. However, the applications of a purely utilitarian approach and rationale to justify all medical research and interventions aimed at promoting the well-being of society poses serious moral and ethical concerns. Society cannot treat mentally incompetent persons as exploitable for the benefit of others as neither the law nor social practice regards profoundly mentally disabled human beings as nonpersons. [241]

[238] Foster C. (2001) The Ethics of Medical Research on Humans, Cambridge University Press, UK
[239] Wellman C (1997) An Approach to Rights: Studies in the Philosophy of Law and Morals. Kluwer Academic Publishers, Netherlands
[240] Cantor NL (2005) Making Medical Decisions for the Profoundly Mentally Diasbles, Massachusets Institute of Technology USA.
[241] Ibid

Clinical research has played a crucial role in the development of modern medical treatments, and they will continue to be necessary as health professionals seek to alleviate existing diseases and improve the survival and morbidity of premature infants. The medical benefits of research in infants are substantial to society and that no satisfactory replacement is readily available. However, for any research to be ethical, the consequences of the research must be considered along with the procedures and the risks that the research subjects are exposed to. While utilitarianism cannot help us with these concepts, the best interests principle does.

6.2 Airedale NHS v Bland and Re A

In this section, I will discuss how the cases of *Airedale NHS v Bland* and *Re A* case provide examples of the law and the courts justifying a society preferred choice that no one involved in the case really wanted to make, which was to choose life or death. Both these cases support the utilitarian concept and illustrate how the court judgements supported societal interest and adapted the fundamental principle of best interest for the individual. In *Bland's* case, the 'utilitarian' argument may be interepreted by counsel that in terms of resources it would be better for society if Bland's life were to be brought to an end due to substantial cost in health care terms, thereby favouring aggregate welfare of others over an individual. Best interest is a highly contested concept and the approach is subject to varying degrees of interpretation depending on individual circumstances.

In *Airedale NHS Trust v Bland*,[242] the court granted a proposed course of action that would eventually terminate life. Tony Bland was a young supporter of Liverpool Football Club who suffered severe brain damage in the Hillsborough tragedy which left him in a persistent vegetative state. The Airedale NHS hospital applied for a declaration that it may be lawful to discontinue all life sustaining treatment and medical support measures designed to keep him alive in a vegetative state, including termination of artificial delivery of nutrition, assisted ventilation, nutrition and intravenous or oral hydration by artificial means. The declaration was granted and Tony Bland subsequently

[242] Airedale NHS Trust v Bland [1993] AC 789.

died. This case, together with the previously discussed *Simms* case, illustrates a judicial willingness to adapt best interests interpretations in order to achieve a desired result. However, by doing so, the courts appeared to have gone against the principle of 'first do no harm' in the case of *Bland* as the decision to discontinue life support would have inevitably resulted in the termination of Bland's life. In the case of Bland, this would have been akin to euthanasia which is illegal in the UK.[243] There are two kinds of euthanasia: (1) active euthanasia, where a deliberate intervention ends a person's life; and (2) passive euthanasia, where a person causes death by withholding or withdrawing treatment necessary to maintain life.[244]

In *Re A*,[245] a case that came before the English Court of Appeal in 2000, Jodie and Mary were conjoined twin girls who were born to devout Roman Catholic parents, who had travelled from Malta to Britain for medical assistance. Jodie and Mary were joined at the pelvis and each twin had her individual heart, lungs, brain and other vital organs. The medical evidence was that Jodie, the stronger twin, sustained the life of Mary, the weaker twin by circulating oxygenated blood through a common artery, and that Mary's heart and lungs were too deficient to oxygenate and pump blood through her own body. With no functioning heart or lungs, Mary's life depended on her ailing sister. If they were not surgically separated, Jodie's heart would eventually fail and they would both die within a few months of their birth. The medical professionals were convinced that Jodie would have a functional and worthwhile life but Mary would inevitably die within minutes as a result of the surgical separation. The parents refused to consent to the operation on religious grounds. It was accepted that the twins were two separate persons each having their own individual human rights. The courts under English law were obliged to make a decision whether or not the surgery could be performed. It was clear that the surgery would kill Mary therefore it would not have been in her best interests, but the surgery was in the best interests of Jodie because it gave Jodie a definite chance of life that would have been otherwise denied. The courts held that "although regard had to be accorded to the parents' wishes, the proposed operation was not a positive act, which would be unlawful because criminal law prohibits any intention

[243] Euthanasia defined by an act of deliberately ending a person's life to relieve suffering is illegal under the English law. See www.parliament.the-stationery-office.co.uk, accessed 24 June 2013.
[244] Ibid.
[245] *Re A* (Children) (Conjoined Twins: Surgical Separation), " 4 All ER 961.

of killing". The medical profession predicted that the surgery would certainly terminate Mary's life and therefore the surgeons, in legal terms, would have intended to kill Mary and would have been liable for murder. English criminal law states that where a person foresees that death is a virtually certain consequence of their action, then they should be regarded by the law as intending to bring about the consequences.[246] The court after much deliberation agreed that surgery could proceed by justifying a defence of necessity in the circumstances. Mary's death was necessary both to save Jodie's life and to restore Mary to the bodily integrity and autonomy which is her own natural right.[247] The courts also absolved the medical profession of all criminal liability for Mary's death on the basis that the doctors owed a duty which they would discharge by means of surgery for defending Jodie from the threat of fatal harm, a threat in this case that arose from the physical burden that Mary had imposed on Jodie through her dependency on Jodie for oxygenated blood.[248] The courts acknowledged that in this case, it was impossible to act simultaneously in the best interests of both twins and agreed that therefore the surgery could be lawfully performed on the basis that Jodie's interests be preferred given that Mary was sadly pre-designated for an early death.[249] Predictably, the surgery went ahead and Mary passed away during the surgery. The parents of Jodie and Mary who had refused consent for the surgery applied to the Court of Appeal for leave to appeal that there should be no medical treatment including separation surgery to either twin without the parents' consent and that the judge's decision was wrong on the grounds that:

> (1) separation of the twins would not be in Mary's best interests and his decision that it would be against the consideration of the evidence, in particular the finding that without separation prolonging Mary's life would be seriously to her disadvantage; (2) separation would not be in Jodie's best interests and his decision that it would be was against the weight of the evidence, in particular the finding that for Jodie's separation meant the expectation of a normal life and he gave insufficient weight to the medical and other problems that Jodie would face if she survived separation; and (3) even if separation would be in the best

[246] R V Woollin. 1 A.C 82, 1999.
[247] Separation 4 All ER 961
[248] Ibid.
[249] Ibid.

> interests of one or both twins it would be illegal, and the judge's characterisation of the operation as the withdrawal of Mary's blood supply and permissible as a withdrawal of treatment was wrong since the operation required could only be characterised as a positive act that would terminate Mary's life.[250]

The concept of a utilitarianism approach can be interpreted as going against the best interests view of providing only a benefit to the individual. It was surprising in the *Re A* case that the courts had almost ignored the fundamental principle of 'do no harm' towards the individuals and supported a 'utilitarian' judgement to find a compassionate solution for *Re A*. Most of the court decisions have concentrated on the benefits for all concerned, given the hope of a satisfactory outcome. Greene noted that "judgements from a psychological point of view, utilitarian judgements were defined as endorsing harmful actions that promote the greater good".[251] Moll and de Oliveira-Souza wrote that utilitarian judgements tended towards favouring the aggregate welfare over the welfare of fewer individuals.[252] In relation to *Re A*, the court's decided that Mary's suffering would continue and eventually she would have died a suffocating death within three months together with Jodie. Thus, it would have been in both Mary's and Jodie's best interests to perform the surgery before the inevitable occurred.

6.3 Applying Principles of Best Interests

In the context of therapeutic research involving infants where one cannot guarantee a better outcome as a result of an intervention - and may in fact have significant risk of a worse outcome as a result of the research intervention - the principle of best interests is not without controversy. This is even more contentious in non-therapeutic research where the individual infant receives no personal benefit from the research participation. It can be further interpreted that parents acting on behalf of their infants be given the choice to adopt a utilitarian approach such that child's interests is for the good of society in the context of research participation. Can we quantify minimal

[250] Ibid.
[251] Greene JD. (2007) 'Why are vmpfc patients more utilitarian? A dual-process theory of moral judgment explains', *Trends in Cognitive Sciences*, 11: 322–323.
[252] Moll J and de Oliveira-Souza R. (2007) 'Moral judgments, emotions and the utilitarian brain' , *Trends in Cognitive Sciences*, 11: 319-321.

risk and 'bend the law' that states it has to be in the best interests of the non-competent individual, as in the case of *Re A*?

The courts may not be in a position to scrutinise medical evidence and what is deemed as best interests from a medical point of view may be only acceptable from a child or parent's perspective when taking into account other factors such as emotional and welfare issues.[253] The right is specific only from a parent-child relationship and only where the child is under the age of majority and the courts are not bound to act in accordance with the parents' wishes. If they were to only act on the parents' wishes then any protective function that the court should uphold over young children, especially infants or children who lack capacity, would be impossible. The ability to override a parent's decisions is dependent on the fact that the parent's role is for the benefit of the child rather than to exercise any power over them as an independent right of the parent. It is also based on a judgment by the court to determine if the parents' wishes should be overridden when considering a parental decision that is disputed. It is said that the courts must exercise its jurisdiction in the interests of children.[254] Notwithstanding judicial statements such as this, it is the best interests test that has allowed the courts to override parental decisions even if they are up to the interpretation of the court and their decision regarded as solely being devoted to the interests of the child that may or may not reach societal expectations. Substitution of parental decisions may be legitimate if the parents are endangering the essential interests of the child. For instance, if the treatment is conventional and routine with low risk to the child, the refusal may result in serious injury or harm to the child. Therefore, in these circumstance, safeguarding the interests of the child with respect to his or her health, justifies overriding any parental decision. It may well be justifiable to rule that the decision of the parents do not meet a reasonable standard. It is recognised that medical intervention outside of the standard treatment of a child poses greater difficulties in assessing best interests for the child such as in therapeutic research involving infants where either being on the treatment or placebo arm of the therapy may have a benefit or it may cause harm. Where there are no clear benefits to the infant, then the best interests test is difficult to apply and in some situations controversial and requires some manipulation of the concept. For example, in

[253] *Re A* (Medical Treatment : Male Sterilisation [2000] FCR 193, CA per Dame Butler-Sloss P at 200.
[254] J v C [1969] All ER 788 HL, per UpJohn LJ at 831.

the case of *Re Y*,[255] a profoundly mentally disabled woman who was found to be the only compatible bone marrow donor to her older sister suffering from leukaemia. *Y* lived in a residential home all her life and had no relationship with her sister but was attached to their mother. The judge ruled in a convoluted reasoning that it would be in *Y*'s best interest to donate the bone marrow to her sister because if her sister were to die, her mother would be extremely distressed. In a case of a donor without mental capacity, and as such extrapolated to infants, the hope and ability to improve the life or health of a sibling is a powerful motivation for the donor's best interests as opposed to losing the sibling altogether no matter how trivial the sibling relationship is described. Is it of any best interests to the donor child if the tissue or organ donation poses moderate risk to his or her health? This can only occur if a broader concept of the best interests test is taken into account to take precedence over the donor's health (for example, a test that would allow procedures which are not against the person's best interest should be lawful). Whether the medical intervention poses a negligible, minimal, moderate or a significant harm to the infant's interests without any reasonable benefit needs to be assessed.

The Children's Act 1989[256] states clearly that when the courts make any ruling in family proceedings they must put the welfare of the child as paramount. In another argument, the courts could make a judgement to choose what the child would choose as an adult in an altruistic manner. It may pose no direct benefit to being a donor and, in effect, may cause harm but it would also save the life of a sibling. To this extent, it may be argued that there is no single one best interests choice for the infant, but there are a range of possibilities that may be equally well chosen and argued for.

6.4 Can we Justify Utilitarianism?

The utilitarian justification for maintaining and contributing to research rests ultimately on a calculation of the whether the minimal risk subjected to infants outweighs the good for society that the research will bring. The utilitarian view is the belief that morally right actions are those that produce the greatest good or greatest

[255] Re *Y (Mental Incapacity)* [1996[2 FLR 787.
[256] Children's Act 1989, section 1(1).

happiness for the greatest number of people.[257] Utilitarianism goes against the best interests view of providing only a benefit to the individual. The opposing view is the deontological approach in believing that certain actions are absolutely right or wrong, regardless of any intentions behind the actions or consequences as a result of the actions. How we marry up the two views when it comes to research involving infants will depend on the processes involved within the research and how much risk the infant is exposed to. The argument for research involving infants is justifiable if the risks involved are minimal such that it will have no long lasting harm for the infant. As long as the choices made do not involve acting to change a system for the worse, a person or infant may demote their personal interests to cause a great deal of good for society. Morality, ethics and other interests come into play in the decision making process. While there are criticisms that utilitarianism has no emphasis on the element of best interests, it is arguable that the life of every person or infant includes a process of balancing personal desires with greater, societal moral considerations.

[257] Scarre, G. *Utilitarianism* (London: Routledge, 1996)

CHAPTER 7: REVIEW AND REVISION OF RESEARCH APPROACH

Shifting the paradigm from protectionism to access is essential in protecting infants, but not at the expense of excluding them from research that may benefit them in the short- and/or long-term. Continuous information sharing and communications with parents and guardians during the consent process must occur and non-therapeutic and therapeutic research should still be pursued in the future. Obtaining consent in any research involving infants is pivotal to ensuring that the research is legitimate. But how do we adequately regulate parental consent and address the issue of infant's participation in research? Should it be invalid for non-therapeutic trials? Do parents actually understand the basis and context of the research they are consenting to on behalf of their infant? Current research regulations remain too paternalistic and in some cases contradictory when it comes to research involving infants. This thesis has argued that there are certain conditions that affect only infants and treatments used for infants have not been properly researched and are based on adult type studies extrapolated inaccurately for use in infants and children. Yet, infants are put in a double jeopardy and disadvantaged in their position by the reluctance to allow infants to participate in research. There should be much broader scope towards recognising the acceptance and the approach for allowing research involving infants. The issue of tightening the consent procedure as discussed is part of a solution. Feinberg[258] argued that there is justification of the right to intervene in a child's life for the sake of the child's future autonomy and their right to an open future. This may include restrictions to legislation which limit the parent's right to consent to participate in research. This kind of approach will be problematic as it does not take into account that the adult would share the same interests as the child in their open future and would act in their best interests. This argument also assumes that there are no relevant differences between children and adults.[259] However, childhood is a vulnerable and formative time when any risk of harm can have serious impact on the well-being of the infant and be potentially long lasting. Potential harms should therefore be assessed carefully before children or infants are put at risk. A more robust approach to allow infants to participate in research - whether it is therapeutic or

[258] Feinberg J. 'The child's right to an open future' in *Freedom and Fulfillment* (Princeton, Princeton University Pressm 1992), 76-98.
[259] Dickenson D. and Jones, D. (1996) 'True wishes: the philosophy and developmental psychology of children's informed consent', *Philosophy, Psychiatry and Psychology*, 2: 287-303.

non-therapeutic - is still ethically defensible. Clinical therapeutic research must relate to the condition from which the infant suffers and that there is no alternative but to use this population at the time for research. They must also be in direct benefit to the involvement of the research. The term 'direct benefit' may seem a little restrictive but there may be some challenges towards the notion of what constitutes 'direct benefit'. For example, a potential 'indirect benefit' if exposing the infant to only minimal risk, may include the future benefit of the infant knowing that he or she had contributed to the research and had made a contribution to the 'greater good'. We can argue that this concept of 'imposed altrusim' constitutes an individual benefit to the infant participating in research, albeit a reason that is difficult to assess.

The discretion and considered decision may lie with the courts to approve the infant's participation over the parents' wishes, considering factors such as whether the risks to the infant are commensurate with the benefits derived, whether the drug has been tested in other populations (such as adults and older children) and what knowledge has been acquired from off-label use. However, these are difficult to assess. Approval should also be sought to affirm the decision to allay researchers' fears of liability and to provide greater oversight to any decisions. Perhaps there should be an independent body that takes into account the best interests of the infant from which the consequence may be a loss of participation in non-therapeutic trials? How do we strike a balance then between benefits to the greater good or the best interests and welfare of the infant in such trial participation? There should be more understanding about how children may be affected by their experiences and, in the case of infants, learning about their effects and responses are important. According to the Declaration of Helsinki, the individual subject must always prevail over science and society. The European Commission had intended to draft legislation forcing drug companies to undertake drug research in children in order that their therapeutic needs are appropriately addressed but it was not captured within the EU Directive.[260] Further proposals were made in the form of incentives, and regulatory and supportive measures with respect to clinical research and development were proposed to ensure that any new development of medicinal drugs for children were

[260] Hawcutt DB and Smyth RL. (2008) 'The new European regulation on paediatric medicines: regulatory perspective', *Paediatric Drugs*, 10(3): 143-6.

researched and adapted to their needs.[261] It is also important to ensure that new medicinal products used in children should have appropriate data, research and safety information must be in place to benefit the child. In 2008, the European Medicines Agency set up a network of research networks, investigators and centres with recognised expertise in performing clinical studies in children called the European Network of Paediatric Research. Their objective was to facilitate studies in order to increase availability of medicinal products authorised for use in the paediatric populations and allowing collaboration with members from within and outside the European Union including academia and the pharmaceutical industry. The network however, does not perform clinical trials or fund studies or research or decide on areas for paediatric research.[262] The purpose of research involving infants should be in the infant's best interests, and any guideline advocating research or intervention should not be "contrary to" or against the child's best interests. Best interests may be interpreted in different ways, such as in examples of non-therapeutic pharmacokinetic drug research, and information on safety is essential in infants and cannot be extrapolated from adult research. It can be argued that the child stands to benefit from the research in the future if the drug being studied continues to be required for the child's health.

The need to offer infants any potential benefits of medical research is important and necessary. Existing regulations and legislation are designed to afford protection to infants who participate in research. The existence of specific ethical guidance, regulations and legislation do not alter the fact that all people, patients, health professionals, and researchers alike have a moral duty of care and a duty to do no harm upon others. It is a general moral principle which forms the basis of the duty of care each person has to prevent any harm coming to others through his or her acts or missions and hence a moral duty to participate in research. For example, we have a moral duty to reduce carbon dioxide emissions to protect future generations. Governments have passed laws to support such utilitarian views. The translation to infants, however, appears to be the opposite where historically there has been a

[261] Edwards SD and McNamee, MJ. (2005) 'The ethical concerns regarding guidelines for the conduct of clinical research on children', *Journal of Medical Ethics*, 421(1): 252-259.

[262] European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA). http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp&mid=WC0b01ac05801df74a

reluctance to involve any infants in research participation, even where there were direct benefits. The expectation to participate in research involving infants is well-founded. If anything can claim a benefit to a greater good, then it is healthcare and the practice of medicine. We have seen this from the history of medicine and production of vaccines and cures to illnesses. It is in everyone's interest that healthcare is of the highest standards. Yet, the highest standards and treatment in healthcare cannot be achieved without medical research and the cooperation of those who can render the research valid. It is not unreasonable that the willingness to participate within the boundaries of minimal risks is a reasonable expectation of everyone, including of parents, to allow their infants to participate in research. If every one of us stands to gain from healthcare resulting from research either past, present, or future, then it stands that we all have a part in our moral duty to contribute to medical research when the risks involved are minimal. Similar to the reasoning that we have a moral duty to enrol in organ donation or in blood donation as it is to do good for society, if each person takes a deontological view that there is no direct personal benefit to themselves, then society will collapse and cease to function. To expect participation in research is to therefore presume that there is a willingness for parents, on behalf of their infants, to do what is reasonably right, and to do what any reasonable, moral person should do when risks of harm are considered minimal. There is indeed a balance to be had between the duty to act in the best interests of the infant with a moral expectation and obligation to the future patients who would stand to gain from the research. Although this approach is neither reflected in the current legislation nor in case law, there is some evidence that the courts may be sympathetic to procedures more beneficial to the community where these are not against the interests of the child and where the risks are minimal. In *S v S,* Lord Reid concluded that the courts ought to permit the blood test of a young child to be taken unless it was proven that it would be against the child's best interests.[263] In *Doherty v McGynn*[264] the Inner House of the Court of Session held that in the exercise of its inherent protective jurisdiction in relation to children, the court could intervene and refuse to admit any evidence if it was not in the child's interests to do so. Both these cases were determined on a case by case

[263] *S v S* [1972] AC 24, HL

[264] *Doherty v McGlynn* 1983 SLT 237. After a hearing on a reclaiming motion, the First Division granted both James Docherty and William McGlynn authority to have blood samples taken from Charlene Docherty, the child to be seriologically tested for grouping 1983 S.C. 202.

basis taking into account the issues as the level of information was given in the decision-making process about risks involved and the interests of the child.

The approach adopted by the RCPCH as an advisory medical college in the UK may be instructive in its guidance on research involving children and infants.[265] The RCPCH states that research is allowed where it poses no greater than minimal harm or risk and where it offers direct benefit to the individual research subject. The difficulty lies in the interpretation that the RCPCH would still support research where it poses no greater than minimal risk but offers no prospect of direct benefit to the individual but may yield information about their condition and where understanding may be advanced about a serious health problem. Any such disagreements about the notion of what constitutes 'minimal risk' should be determined by independent ethics committees to scrutinise all research proposal prior to any approval for recruitment. Brazier argued that judges and courts should not be the final arbiters of acceptable research practice, but suggests that the establishment of any code of practice in the context of research underpinned with statutory requirements of where consent can be given and by whom, should be overseen by independent expert scrutiny such as research ethics committees who will ensure that parents are given fully informed consent and that the consenting procedures are not flawed as discussed in Chapter 5. She also suggests, where children are concerned, it is mandatory that a paediatrician and other relevant health professionals be called upon to be part of the independent ethics panel.[266]

[265] See n153.
[266] Brazier M. *Medicine, Patients and the Law* (London, Penguin, 2003).

CHAPTER 8: CONCLUSION

Clinical research involving infants is important and required for the reasons explained earlier. Understanding and complying with the special ethical and regulatory protections for infants constitutes challenges to research and such challenges underscore the need for those reviewing research protocols that include the subgroup of children who lack capacity to make decisions on their own, to have adequate expertise in different areas of child health and research. Clinical trials, whether they are categorised as therapeutic or non-therapeutic, must be scientifically sound. The fact remains that infants are not adults and some conditions only affect infants and that a significant proportion of drugs prescribed today for infants remain untested. Any trial that exposes the participant to significant risks or burdens without yielding any meaningful results and that do not test the hypotheses are deemed as unethical. Randomised controlled trials are often considered the best way to provide the most meaningful results as participants are randomly exposed to either a placebo versus the treatment, or conventional treatment versus the novel treatment. The participant in this case stands to gain from being in either arm of the trials which are conducted to determine which provide the best results. However, only a handful of cases have addressed the issue of non-therapeutic research in non-consenting and non-competent subjects, and the results have similar concerns pertaining to the argument of what risk is deemed as acceptable, and whether the research in question offered some benefit to the subjects and therefore may be regarded as therapeutic in nature. When efficacy data from any adult research trial cannot be extrapolated to the target group of population - such as infants - then non-therapeutic research is required.

Such debates are open for further factual developments and it would be important for communities such as legal and scientific research practitioners to collaborate and to closely examine, understand, analyse and address the ethical and legal issues that so concerns the courts. The framework does not currently exist to deal effectively with ethical issues that arise as infants become research subjects in non-therapeutic research. This thesis has attempted to reconcile the arguments for and against non-therapeutic research involving infants and deliver a review and revision of

research methods and guidelines surrounding the use of infants in non-therapeutic research. It is clear that scientific advancement through the conduct of research has improved the quality of lives. Vaccines produced against diseases, new technology to understand functions of the body, new medications to eliminate infections and disease progression have all been the result of carefully conducted research and the dedication of scientists. Yet the position of infants has been neglected in previous and recent legal and ethical regulatory frameworks and guidance, and we need to bolster their position such that infants are more widely considered in an optimal manner to allow their engagement in both therapeutic and non-therapeutic research where there is minimal risk. Research involving infants must continue, but it should be carried out within strictly circumscribed limits to ensure that infants are not unduly exposed to greater than minimal harm or risk.

A more balanced approach is needed that is necessary and timely to justify a research proposal to include an infant in a clinical trial, rather than have blanket avoidance because of a fear that it may be unethical due to age. There is a need to find a more useful approach towards research involving infants, and to be persuaded that there is a common good argument that follows finding such an approach where there is an expectation that everyone albeit infants should participate in research within proper governance and ethical regulations to safeguard all participants' interests. Researchers should recognise the vulnerability infants when they are recruited to clinical trials and should remain impartial whilst ensuring that parents are given fully informed consent to decide on their infants' behalf. Infants and children should be afforded the same equal opportunities to benefit from research as adult subjects. The pursuit of knowledge is valuable but it is not the ultimate goal. Research and its acquisition must be underpinned by core values and unified within ethical and legal regulations. The world must safeguard against a country repeating the unethical and heinous crimes from the Nazi experimentation on human subjects. Children's rights are universal and cover the span of childhood up to the age of eighteen. Parental rights and sole parental consent can deter rather than facilitate the best interests of the child and some professional guidelines on consenting for incompetent and vulnerable infants may be deemed as too permissive. Interestingly, Friedman Ross argues that the best interests standard is too individualistic and does not allow parents to make decisions which can take into account

the interests of the family as a group. She states that "to hold parents to a best interests standard which cannot accommodate intra-familial trade-offs is to misunderstand the role of parents and the value of the intimate family".[267] The best interests standard is not such a viable criterion that conflicts may also arise between two parents who may have divergent views on what are the best interests for their infant. Parents act, therefore, as surrogate decision makers who give or refuse permission for treatment on the basis of what they believe to be in the child's best interests. It is arguable that parents have a wide discretion as to what may or may not be in the infant's best interests and they are not bound to meet the best interests as the courts have interpreted it. Furthermore, the application of the best interests principle is contentious and problematic when the research intervention may be of no benefit to the infant participating in the research even though the involvement of infants who represent a unique population may be vital in improving the care of future populations of infants. However one interprets the best interests test, there are still many unknown factors and conflicting evidence as to what will best serve the welfare of the child. The application of the best interest test is not straightforward and a wider interpretation of the best interests test may allow the test to be stretched and manipulated in order to achieve the desired results. The best interest test can be constructed to accommodate social interests as we have seen in the *Re A, Re Y* and *Simms* cases that has been examined. They are examples where the best interest test can be re-calibrated to balance minimal risk versus benefit to others. We may justify this approach that may be in conflict with the direct best interests principle, and the opinions of the medical profession have been regarded with a greater willingness of the courts to allow other factors to override the interpretations involved in decision-making about the welfare of children.

The conventional approach to the best interests argument has problems in the context of research involving infants and is particularly difficult to apply in certain situations such as procedures or intervention that has no therapeutic benefit to the infant. It will require some stretching of the concept to justify such an approach which is already prevalent in healthcare practice and research communities today. Legal and ethical guidance on how we place the infant's best interests and balancing of risk and

[267] Ross, LF. (ed.) *Children, Families and Healthcare Decision-Making* (Oxford, Clarendon Press, 1998), 32.

harm into the context of research is required and particularly the question whether the best interests test is appropriate in deciding the issues discussed. Earlier this thesis provided an outline and assessment of the legal and ethical framework for recruiting infants into clinical research, which shows a clear gap in the laws and ethical guidelines surrounding recruitment of infants into therapeutic and non-therapeutic clinical research trials. Research involving infants raises difficult issues in relation to ethics, social policy and law but it is essential that research is carried out in infants.

There is a paucity of information or regulation on the extent of the infant's rights to protection from possible harm and the ethical issues surrounding sole parental consent on behalf of the infant, as well as exploring conflicts of interests amongst researchers when actively recruiting infants into research. The core issues which emerge from the application of current research and legal frameworks make the case for a clearer articulation of the content and principles of current standards that exist to include the role of research involving infants. The thesis has clearly shown where the current gaps are: in the law, its policies and the ethical guidelines on research involving infants. It has drawn upon case studies and anecdotal experience as a clinical researcher involved in the recruitment of infants into therapeutic and non-therapeutic trials.

Despite the current guidance from ethical and legal perspectives as outlined earlier, it is clear that there is a loud silence surrounding research involving infants. We need a more rigorous approach that can be adopted to ensure that infants rights are protected but they are allowed to continue to participate in research weighing the benefits and risks at stake from the research, and ensuring that risks are indeed minimal and distress to the infant is trivial with their parents fully informed of the consent procedures. This may be achieved by ensuring that there are sufficiently sophisticated assessments, consenting procedures and allowing a presumption that every infant may wish to participate in research that does not necessarily directly benefit themselves as individuals but would benefit their population as a whole. Ethical guidelines should facilitate research in children in a wider context where full information has been given to parents or legal guardians including objectives, risks, inconveniences, conditions and rights to withdraw. Ethical standards for participation in research require that the agreement to participate be freely given; that is, it should not be either coerced or

unduly influenced by psychological, financial or other pressures. There must be no financial inducements, conflicts of interests or any other compensation for participation apart from compensation due to injury or loss. The major concern about payments related to research participation is that they may unduly influence and distort decisions about research participation made by individuals in their own right or by parents on behalf of their child. Some types of payments to parents such as reimbursement for reasonable expenses like travel are necessary for participation in research. Any other form of payments that involve paying parents for permitting their child to be exposed to a greater research risk are not ethical nor lawful under the Clinical Trials Regulations.[268] Compensation to parents for lost wages or time may be appropriate under carefully scrutinized circumstances. Pain and discomfort, fear and any foreseeable risks must be minimised and scrutinised by design of the trial with age of the child in mind, and with risk thresholds and degrees of distress defined and monitored closely in the conduct of the research.

This does not advocate that all infants be subject to undue risk nor for those close to them to be excluded from being involved in the decision-making within the research process, but for parents to be fully informed of research processes and be given the responsibility to make decisions on behalf of their infants. There cannot be a deontological view when it comes to research involving infants as there are no absolute right or wrong approaches with regard to research participation given the difficulties and ambiguity in current legal and ethical guidelines on research. Parents are allowed on a daily basis to make decisions for their child and they have the responsibility to determine what they believe to be in the best interests of their infant, what is appropriate and subject to harm limitations. On a daily basis even the courts establish a balancing of harms and benefits to children in making decisions concerning their welfare. So to this extent, the approach to research involving infants should be weighed in a similar regard. We should not be asked to declare a single response as to what is best for the infant when there are a range of reasonable responses that could be made. It is possible to reconcile legal guidelines with the rights of the child, and to serve the best interests for

[268] UK Medicines for Human Use (Clinical Trials) Regulations 2004, see Regulation 15 and Part 1 of Schedule 4, para 9 and 10).

the child and the greater good of the community. The correct approach is not to give up on a best interests approach but to try and minimise its pitfalls.

Parental consent to research interventions are intended directly to benefit the child to some extent, but similarly the extent of the risks should be sufficiently small to mean that the research can be reasonably said not to go against the child's interests.[269] Valuable and important research in certain circumstances can only be done in infants because of the particular aims of the research study. However, when choice of age is possible, older children should be involved in preference to younger ones, and research in children or infants should only be undertaken if the research in adults were not feasible. The academic and scientific community must recognise the importance of sound ethical research conducted in infants today as well as scientific progress if it is to sustain the support and trust of policymakers and the public including parents who consider the enrolment of their infants into research. The benefits that medical or clinical research has brought to infants, children and adolescents are remarkable with recent decades proving that medical research has helped change medical care and public health practices in ways that have saved or lengthened the lives of tens of thousands of children around the world and prevented illness or disability worldwide. However, utilitarian arguments for research involving infants are contrasted with deontological views of a focus on the infant's rights and best interest alone. A narrow reading of the best interests approach cannot possibly run in today's approach to research involving infants, but a wider interest of society as well as the individual's interest but develop in line with a changing society. There is a moral duty for parents to allow their infants' participation in research and there is also a duty to do no harm. Where risks are deemed as minimal, it is fair to expect a utilitarian view that everyone should contribute to healthcare in a way that would benefit all for a greater good. Although the existing legislation and ethical guidance are focused to provide protection to individuals involved in research, there is a general moral principle to expect each and every person to be willing to participate in research that will benefit healthcare especially where the risk of harm is minimal or non-existent. This approach is not reflected in the law or the current legislations for research although there is some evidence that the courts may be

[269] McKechnie L and Gill AB. (2005) 'Consent for neonatal research', *Arch Dis Child Fetal Neonatal Ed*, 91(5): F374-6.

sympathetic to the idea that parents may consent to procedures that may benefit the community when they are not against the child's best interests. Each case is often unique and determined by its own merits within a general framework of legal and ethical guidance and principles. The lack of good research will have societal implications for future healthcare. In conclusion, the proposals and arguments contained in this thesis aim to strike a balance between appropriate protection and empowerment to ensure that the interests of infants are not undermined, together with the needs of the society and research communities by allowing parents to be responsible in allowing their infants to participate in research with minimal risk for the benefit of the greater good.

Note:

Writing this thesis has been a challenge as I realised that I had embarked on a task that was interdisciplinary with very different ideological approaches, as well as being influenced by both my personal and professional history.

I hope that the key conclusions and recommendations not only raises an awareness of the issues described but also represent a balanced opinion for consideration by law makers, policy makers, and health professionals to assist parents and their children in future research participation.

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APPENDIX

A. Mental Capacity Act

The Mental Capacity Act applies to England and Wales only. As of 1st of October 2007, medical research covered by the Act in section 30 to 32, cannot include any people who lack capacity to consent to the research unless:

- The research has the approval of a research ethics committee recognised by either the Secretary of State or the Welsh Assembly Government as appropriate.
- The researcher considers the views of carers and other relevant people.
- The research treats the person's interests as more important than those of science and society.
- The researcher respects any advance decisions or expressed preferences of a person who lacks capacity and any objections the person makes during the research
- The research must be connected with an impairing condition affecting the patient or his/her treatment. There must be reasonable grounds for believing that research of comparable effectiveness cannot be carried out if the project has to be confined to, or related only to persons who have capacity to consent to taking part in it.

The research must have the potential to benefit without imposing a burden that is disproportionate to the potential benefit or intended to provide knowledge of the causes or treatment of, or of the care of persons affected by, the same or a similar condition.

B. Good Clinical Practice and Related Legislation and Directives

The EU Directive 65/65/EC[270] resulted in the formation of a Committee for Proprietary Medicinal Products (CPMP), which first assessed whether candidate products complied with Directive 65/65/EEC after the postnatal side effects of thalidomide in the treatment of pregnancy emesis became a worldwide concern, and the requirement of licensing of all medicinal products was mandated in 1965 for all member states. In 1975, EU Directive 75/318/EEC stated that each member state be required to ensure that the submission of safety and efficacy for marketing authorisation and Good Laboratory Practice (GLP) were formed encompassing the principles of non clinical testing of pharmaceutical products and the requirements of GCP in conducting research. It stated that "all phases of clinical experimentation shall be designed, implemented and reported in accordance to GCP 75/318/EEC". This enforcement would appear to apply to non-therapeutic research and its guidance on conduct. In 1991, the European Commission published the 'Enforcement of the EEC Note for Guidance: Good Clinical Practice for Trials on Medicinal Products in the European Community'.[271] The Directive 75/318/EEC was not legally binding until a modification to the Council Directive in 91/507/EEC.[272] The EU Directive in 91/507/EEC required all European member states to bring into force the laws and regulations and administrative provisions necessary to comply with the Directive that requests all clinical trials to be designed, implemented, recorded and reported according to GCP policies. In 1996, the International Conference of Harmonisation (ICH) issued guidelines for GCP- the ICH 1996 which was developed to promote international consensus on mutual regulations on clinical trials and marketing authorisation procedures. It was later adopted by the Committee for Proprietary Medicinal Products (CPMP, now the CHMP) and formally accepted as a standard in European Union states in 1997, thus replacing the previous EU GCP guidance. Directive 2001/20/EC of the European Parliament on laws, regulations and administrative provisions relates to the implementation of GCP in the conduct of all research for human use. The community code related to medicinal products for human

[270] Commission decision for the granting of marketing authorization for the medicinal product for human use OJ No L 214 of 24th August 1993, 1.
[271]Good Clinical Practice 2013 accessed 15th April 2013 at www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/index.htm.
[272] Directives are binding on Member States insofar as they have to implement or amend national measures to give effect to the main aims and objectives of the Directive, but such have a degree of flexibility as to how to achieve this in the light of their individual domestic context.

use (2001/83/EC) was later amended in 2003 by 2003/63/EC stipulating that all clinical trial research data used for marketing authorisation applications in the European Union are required to be conducted in accordance to the GCP.

Table 1: History of Good Clinical Practice (GCP) and Related Legislation and Directives[273]

Year	***Event***	***Comment***
1947	Nuremberg Code	Principle of informed consent
1964 (revised 1975, 1983, 1989,1996)	Declaration of Helsinki	
1965	65/65/EC	Licensing of medicinal product
1968	Medicines Act	
1975	75/318/EEC	Safety and efficacy requirement for marketing authorisation. GLP became the principle of non-clinical testing
1991	91/507/EEC	GCP in EEC
1997	CPMP/ICH/135/95	ICH GCP published by Committee for Proprietary Medicinal Products
2001	2001/20 EC	EU Clinical Trial Directive
2001	2001/83/EC (part 4, B1)	Community code on medicinal product, requirement of GCP in conducting clinical trials
2003	2003/63/EC	Amendment on 2001/83/EC. Part 1, 5.2.c defines holding period of essential clinical trials document
2003	2003/94/EC	GMP requirements for IMP
2003	EUDRACT	EUDRACT database guidance note
2003	Annex 13	Manufacture of IMPs

[273] Good Clinical Practice 2013 http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/index.htm. *Accessed April 15th 2013*

2004	2004/27/EC (13)	GCP requirement for clinical trials outside the EEA
2004	SI 2004/1031	The Medicines for Human Use (Clinical Trials) Regulation's 2004
2005	2005/28/EC	Guidelines for GCP
2006	SI 2006/1928	The Medicines for Human Use (Clinical Trials) Amendment Regulation's 2006

EEA, European Economic Area; GLP, good laboratory practice; GMP, good manufacturing practice; ICH, International Conference on Harmonisation; IMP, investigational medicinal

C. The Status of Unmarried Fathers

The Welfare Reform Act 2009 contains provisions that mandate compulsory joint birth registration for unmarried fathers. The idea was that if unmarried fathers will be jointly named on their child's birth certificate with the mother, ensuring these fathers had parental responsibility for their children would also encourage them to play a role in the child's life and maintain the child.

In Section 56 and Schedule 6 of the Welfare Reform Act 2009, in force since May 2012. These sections make significant amendments to the Children Act 1989.[274] The provisions impose a duty upon an unmarried mother to provide details of her child's father when she registers the birth (unless certain conditions apply).[275] The Act included provision for enabling the registrar to contact the person identified by the mother. If he confirms that he is the father, his name will be entered on the register, granting him parental responsibility.[276] The Act also includes provision for the father to contact the registrar to identify himself as the father of a child and, upon confirmation of this by the mother, for his name to be added to the register.[277]. The 2009 Act threatens a fine of £200 and a prison sentence of 7 days for perjury if mothers provide a false answer.

Exceptions are however included, and these include exceptions to protect women in certain circumstances where they are at risk of, or in fear of, harm from disclosure. So while the Act is considered highly controversial by many and is designed to compel a mother to name the father, the list of exceptions is extensive, including the exception that the 'mother does not know the father's identity' (c). Thus, if a mother wanted to conceal the identity of the father she can simply give this reason to the registrar and there is not much the registrar can do but leave the name of the father blank.

For further discussion of the provisions of the Act see:

A Bainham, 'What is the point of birth registration?' Child and Family Law Quarterly (2008); 20(4) : page 449

[274] For further information on the background to these provisions see: *Joint birth registration: recording responsibility* (Cm 7293) June 2008.
[275] Welfare Reform Act 2009 Schedule 6 Part 1 para 4 amending s 2 Births and Deaths Registration Act 1953. There are exceptions to this duty such as *inter alia*, where the mother does not know the identity of the father or fears for her safety if he were to be contacted (s 2B(4) Births and Deaths Registration Act 1953 as it will be amended by the Welfare Reform Act 2009)
[276] S 2C Births and Deaths Registration Act 1953 as it will be amended by the Welfare Reform Act 2009.
[277] See s.2D and 10B Births and Deaths Registration Act 1953 as it will be amended by the Welfare Reform Act 2009.